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DEVELOPMENT OF AN ARTIFICIAL KIDNEY

Experimental and Clinical Experiences

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Assisted by
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USING heparin as an anticoagulant, attempts were made to clear the blood stream of toxic substances by transplantation of a kidney from one animal to another and from one species to another. This work was done in 1933, 1934 and 1935, with moderate success.[1] The objective in this present investigation was to prevent a patient's dying of acute toxemia in such conditions as acute poisoning by mercury and phenol, in toxemia of acute infection, such as nephritis or pneumonia, with oliguria or anuria, as well as in acute anuria following blood transfusions, administration of excessive sulfonamide drugs, eclampsia and toxemia of pregnancy, severe cutaneous burns, induced abortions and acute injury to ureters and kidneys from calculous obstructions, reflex or otherwise, or operation.

It seemed possible that if the patient could be protected from death from toxemia in such conditions, after a time there would be sufficient recovery in a number of cases so that the affected kidneys might resume function.

It was with satisfaction, therefore, that experimental results to justify this thesis were noted and that clinical evidence has supported the claim. Also, it has been demonstrated repeatedly that the apparatus herein described works smoothly for long periods and that it performs the functions for which it was developed.

Many other workers have embarked on similar investigations, including Abel, Rountree and Turner,[2] Thalhimer,[3] Best and many

Read at the fourth annual meeting of the Central Surgical Association, Chicago, Feb. 21, 1947.

1. Murray, D. W.: Heparin in Thrombosis and Embolism, Brit. J. Surg. **27**: 567, 1940.

2. Abel, J. J.; Rountree, L. G., and Turner, B. B.: Tr. A. Am. Physicians **28**:51, 1913; J. Pharmacol. & Exper. Therap. **5**:275 and 611, 1914.

(Footnotes continued on next page)

others on this continent, but to our knowledge the work has not been developed to a point where it was a proved effective clinical method of treatment. The one exception is the work of Kolff [4] in Holland. We were not aware of his work, and only after the war did information on his work arrive. His monograph gives evidence of his extensive treatment of patients, with some good clinical results. Our efforts have been going on apparently simultaneously and independently. It was interesting, therefore, to compare the methods and the material used and to note the different avenues followed, which evidently converge fairly closely toward the same goal of end results.

The principal aspects of the artificial kidney are: (1) a dialyzing membrane which is selective in allowing the passage from the blood stream of some substances and not of others, namely, nonprotein nitrogen and other toxic substances, (2) a method of circulating the blood through this extrinsic system and (3) protection from removal of necessary substances from the blood stream.

It was after extensive and arduous trials and experiments that we finally arrived at the present setup, which works satisfactorily both experimentally and in clinical patients.

The following summary includes some of the events which led to the development of the apparatus and might be termed the evolution of this machine.

1. The first method was the circulation of arterial blood with return through the venous side through several coils of cellulose acetate tubing (sausage casing) bathed in warm tap water. This tubing was 1 inch (about 2.5 cm.) in diameter and presented the primary disadvantage of the ratio of volume to surface area. Also the size of the tubing allowed too much escape of the animal's blood before there was sufficient return, if a reasonable length of the tubing were used. In this way the animal really had hemorrhage into the tubing. Filling this with blood beforehand overcame the difficulty.

2. Later, with considerable effort, tubing ½ inch (1.27 cm.) in diameter was obtained, and with this somewhat better results were obtained. Later, from the Visking Corporation of Chicago, ¼ inch (0.63 cm.) tubing was obtained, and with this fairly satisfactory results could be achieved.

3. With fairly long sections of this tubing in vitro we were able to demonstrate that (fig. 1) there was some passage of nonprotein nitrogen substances through this membrane and that the larger protein molecules did not pass.

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3. Thalhimer, W.: Artificial Kidney and Experimental Exchange Transfusion for Reducing Azotemia, Proc. Soc. Exper. Biol. & Med. **37**:641, 1938.

4. Kolff, W. J., and Van Noordwijk, J.: The Artificial Kidney, Kampen, Holland, J. H. Kok N. V., 1946.

4. To diminish the volume of these tubes it was attempted at first to pass the tubing through a series of wire cells containing the dialyzing tubes.

5. Next, concentric wire cylinders, between which the tubes were partly compressed, were used.

6. Then, a wooden reel was tried, on which the coils could be assembled fairly quickly. This did not control the volume satisfactorily.

7. Next, it was decided to coil the tube around a small platform, and on each side plastic perforated sheets were applied and bolted together to compress the tubing in the coil. These were in turn found to be unsuitable, because of the bulging under the pressure of the fluid in the coil.

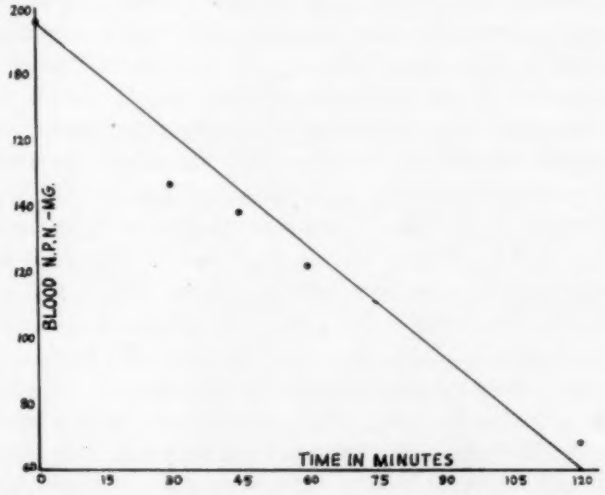

Fig. 1.—In vitro experiment on human blood, showing the fall of nonprotein nitrogen during two hours of dialysis in the artificial kidney (length of tubing 25½ feet [about 777 cm.]). In the two hours 2.3 Gm. of nonprotein nitrogen was recovered. No proteins came through.

8. Then, sheets of the plastic plates were replaced with wood, and these were found to warp.

9. These were replaced with aluminum steel plates, which were bolted together with a thin definite spacing between them. This worked moderately well, but was finally discarded for a vertical wire mesh cylinder.

10. A vertical wire mesh cylinder around which the tube was wound in spiral fashion and held in place by cross pieces of wood finally gave the best result with the ¼ inch (0.63 cm.) tubing, and lengths up to 135 feet (about 44 meters) of tubing could be used satisfactorily, giving a fairly high rate of dialysis.

SOURCE OF BLOOD FOR DIALYSIS

The next problem to be solved was that of a method of circulating the blood. It was decided that using an artery as the propelling force had many disadvantages: 1. The artery could be used only once. If further attempts were to be made, another vessel would be required. 2. The pressure in the system was such that there was not a satisfactory return of the venous blood by this type of pressure. Moreover, the animal tended to act as from the result of hemorrhage from arterial bleeding.

In all these methods, of course, it is obvious that the animal was highly heparinized [5] to make sure that there was no clotting or thrombosis in the system, at the points of intake or output or in the animal itself.

It was decided to attempt to develop a system in which the blood could be taken from the venous system and then returned through another point in the venous system. On this basis, blood was taken first from femoral veins and then external jugular veins, but it was observed that with any pump system which produced suction the vessel collapsed and acted as a valve over the tube. To overcome this difficulty a catheter of fairly large diameter was passed through the femoral vessels and into the inferior vena cava or into the right side of the cardiac region. From this any quantity of blood could be removed by aspiration without any interference or obstruction, and it could be returned readily to a vein on the opposite side. This seemed to have many advantages: 1. There was no ill effect on the blood pressure of the animals, simulating hemorrhage. 2. The quantity of blood removed could be controlled accurately, which was not the case when an artery was used. 3. The unoxygenated venous blood was circulated through the system, and, therefore, more impurities were available for dialysis by this method. 4. The blood was not oxygenated, and it was easy to add oxygen to it as well as dialyze it during the circulation through the system of tubes.

PUMP SYSTEM

The next problem was in providing a circulating pump system which would not damage or crush the blood corpuscles, would not produce hemolysis, would work smoothly and would not become plugged and clotted with fibrin.

1. At first, the blood was drawn into a flask, then circulated through the dialyzer and then returned to the venous system by gravity. 2. Next, a syringe piston was used as a pump, with intake and outlet valves on glass seats, but it was early demonstrated that in spite of a high degree of heparinization, the spinning of these valves and the passage of the blood through the small apertures tended to cause some collection of fibrin and interfere with the function of the system.

5. Murray, G. D. W.: Heparin in Thrombosis and Blood Vessel Surgery, Surg., Gynec. & Obst. **72**:340, 1941.

3. A rotary pump effect was used, but this was only moderately satisfactory. 4. Finally, a pump system was used whereby a rubber tambour was inflated and deflated by the action of the piston-syringe attached to an electric motor. Rubber intake and outlet valves gave good effect from the pump, so that smooth circulation without injury to blood and without clotting and deposit of fibrin or platelets could be carried out for many hours at a stretch.

EXPERIMENTS IN INCREASING DIALYSIS

Many efforts were made to increase the rate of dialysis through the membrane: 1. The best and most obvious way of increasing dialysis was by increasing the length of the tubing used. In the experiments lengths up to 35 feet (about 1,067 cm.) were used satisfactorily, and it would seem possible to increase this length considerably more with still more beneficial effect. 2. It was thought that by attempting to reduce the atmospheric pressure surrounding the tubing an improvement in dialysis might be obtained, but results of these experiments were not satisfactory. 3. By increasing the pressure within the dialyzing tubing it was thought that there might be some increase in the dialysis, but again this requires further study to be certain of the effect. 4. Some investigation to see whether the work described by McBain and Kistler [6] would apply under these conditions was carried out. They indicated that the use of 64 per cent zinc chloride solution would stabilize the apertures in the membrane and would increase the rate of dialysis. Extensive tests were made with this, which covered a period of several months. Figures 2 and 3 show the results of some of the experiments with this tubing. It was our conclusion, finally, that while there was some beneficial effect in the rate of dialysis early in the exchange, in the final results there was not a great difference. It did not seem to be a sufficiently great difference to justify or warrant the effort and trouble of treating the tubing, and for that reason the method was discarded and the untreated tubing was used. It was noted in our experiments that the use of zinc chloride with adequate washing afterward did not seem to produce any toxic effects in the animal.

THE DIALYSATE

The next problem in relation to the protection of the animal against the removal of substances which are necessary for life involved a great deal of work and was the most difficult to solve. It was observed that if an animal's blood were dialyzed through this machine with a sur-

6. McBain, J. W., and Kistler, S. S.: Membranes for Ultrafiltration, of Graduated Fineness Down to Molecular Sieves, J. Gen. Physiol. **12**:187, 1928; Hydration of Sucrose in Aqueous Solutions, J. Phys. Chem. **33**:1806, 1929; Ultra Filtration as a Test for Colloid Constituents in Aqueous and Non-Aqueous Solutions, ibid. **35**:130, 1931; Membranes for High Pressure Intrafiltration, Tr. Faraday Soc. **26**:157, 1930.

rounding bath of tap water within five to seven minutes the animal showed striking clinical changes. The rate of breathing was accelerated to the point of violence. There were shock and collapse, and the animal died within a period of seven to fifteen minutes.

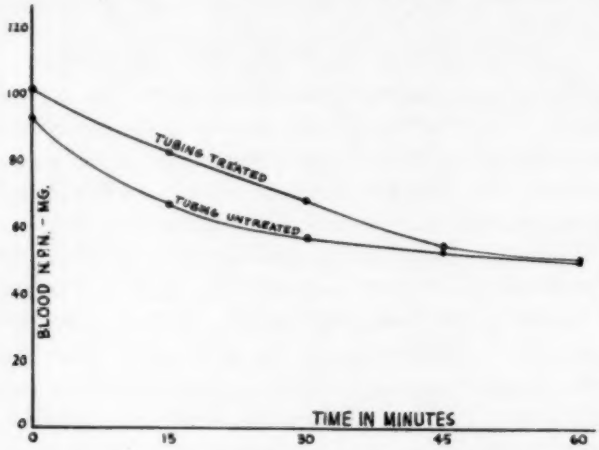

Fig. 2.—Graph showing the relative efficiency of tubing treated with zinc chloride and untreated tubing in removing nonprotein nitrogen from human blood (in vitro).

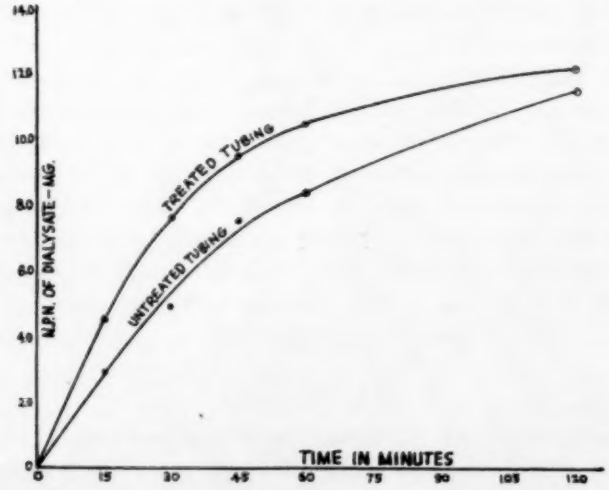

Fig. 3.—Graph showing the amount of nonprotein nitrogen recovered in the dialysate when dialyzing urea from an aqueous solution in vitro and the rate of dialysis with untreated tubing as compared with tubing treated with zinc chloride.

We were not certain at this stage whether important substances, such as epinephrine, pituitrin, insulin, heparin and so on, were being removed and whether the animals were going into shock on this account. As the chemical tests for some of these substances are difficult

and uncertain, we were not convinced by chemical analysis whether such was the case or not. However, we arrived at our final conclusions by the following methods.

During dialysis it was demonstrated that the animal had an increasing concentration of hemoglobin (table 1) and that he showed evidences of loss of water. It was decided, therefore, to balance the

TABLE 1.—*Results of Dialysis in Vivo in Blood of Dog During Two Hundred and Twenty Minutes of Perfusion, Using Warm Running Tap Water as the Dialysate*

Sample Number	Time of Test	Nonprotein Nitrogen, Mg./100 Cc.	Chloride *	Hemoglobin, per Cent
1	Before dialysis	40	...	91
2	After 40 min.	43	562	95
3	After 90 min.	44	...	..
4	After 130 min.	56	...	..
5	After 160 min.	60	...	..
6	After 200 min. (after 4 Gm. urea given intravenously)	100	...	..
7	After 220 min. (blood entering artificial kidney)	54	464	105
8	After 220 min. (blood leaving artificial kidney)	41	360	..

* There is a continuous fall in the blood chlorides and a rise of hemoglobin, indicating a loss of chlorides and of water.

TABLE 2.—*Changes in Blood* in a Dog After One Hundred and Ninety Minutes of Perfusion with the Artificial Kidney*

Sample * Number	* Time of Test	Blood Nonprotein Nitrogen, Mg./100 Cc.	Hemoglobin, per Cent	Red Blood Cell Count
1	Before dialysis	37	90	5.5
2	After 15 min.	40	79	5.4
3	After 70 min.	35	78	5.1
4	After 130 min.	37	91	6.1
5	After 190 min. (blood leaving artificial kidney)	42		
6	After 190 min. (blood from artery, after contents of dialyzer returned to animal †)	37		

* The dialysate was 20 liters of isotonic solution of sodium chloride.
† With isotonic solution of sodium chloride as the dialysate the animal was in good condition after one hundred and ninety minutes of dialysis.

dialysate by surrounding the tubing with some of the normal substances in blood, as indicated in Ringer's solution. It was observed that on addition serially of each of these substances we could overcome one or the other of the difficulties and could carry on a dialysis without having these disastrous effects on the animal. When the chlorides, calcium, magnesium, potassium, sodium, phosphate, carbonate and sugar were balanced in turn, we observed that these disastrous effects in the animal did not occur (table 2). It was observed in the preparation of our dialysate that with the potassium left out the animal suffered ill effects and when potassium was added he was protected against these effects.

Results were similar with the other salts and sugar. Variations in the p_H also caused alarming results. It was necessary to add the bicarbonate to the solution to preserve the p_H at a level of about 7.3. With the dialysate at this p_H there was no change in the blood p_H during or after dialysis.

However, as both quantitative and qualitative tests for some of these chemicals are difficult and unreliable, it was difficult or impossible to prove the specific effect of the lack of potassium, calcium and so forth, although the experimental proof of this seemed to be adequate. Finally, a bath solution similar to that used by Seligman was used. It contained sodium chloride, calcium chloride, magnesium chloride, potassium chloride, sodium hypophosphate, sodium bicarbonate and dextrose in physiologic amounts. This solution was well buffered, but required a certain care in mixing and autoclaving to prevent precipitation of insoluble salts.

TABLE 3.—*Composition of Dialysate (Eighteen Liters of Perfusion Fluid)*

Ingredient	Amount, Gm.
NaCl	144
$CaCl_2$	1.8
$MgCl_2$	1.8
NaH_2PO_4	0.9
Dextrose	27.0
KCl	3.6
$NaHCO_3$	18.0

TRANSFUSION OF BLOOD

The next problem was the fact that in a smallish or medium-sized animal there was so much loss of blood into this machine before any was returned that the animal was left with the saline solution in his circulating system and all his blood was out in the apparatus before any was being returned. However, this was overcome by filling the machine with suitable blood for the animal. When this was done, the circulation could be carried on indefinitely without ill effects.

Many of our earlier experiments were carried on in vitro by circulating blood and other solutions through the machine and by placing substances in the circulating fluid which could be detected in the surrounding dialysate (table 4). Next, in a normal animal, with the fluid circulating, 4 Gm. of urea were injected, and the rate of removal of this was determined as indicated in table 1. With the tendency of urea to form a closer relationship in the blood of dogs, it was probably not as fair a test of dialysis as might occur in human beings, in whom the urea is separated more readily and is more easily dialyzable. However, this did demonstrate the rate of removal of nonprotein nitrogen substances from a normal animal.

UREMIA IN ANIMALS

The next problem was to produce azotemia in an animal, so that the effectiveness of the apparatus could be assessed under these conditions. Bilateral nephrectomy was observed to involve a number of uncontrollable factors, and the uremia so produced was so severe and associated with such poor resistance in the animal that it did not lend itself to these experiments. A more gradual onset of uremia was desirable and thought to be more comparable to the clinical disease in patients.

The chemical production of oliguria and anuria were investigated, but no completely selective uncomplicating poison which seemed suitable was encountered. Most of the work done on specific renal damage involved the perfusion of the kidney by exposure and cannulation of renal vessels.

TABLE 4.—*Changes in the Blood and Plasma in a Dog During Two Hours of Perfusion by the Artificial Kidney*

Time of Test and Direction of Flow	Blood Nonprotein Nitrogen, Mg./100 Cc.	Plasma Count, Mg./100 Cc.
After 20 min., perfusion, going into apparatus	39.5	410
Fifteen Grams of Urea in Isotonic Solution of Sodium Chloride Added		
After 80 min., going into apparatus	156.2	415
After 80 min., coming out of apparatus	122.6	439
After 2 hr., going into apparatus	98.0	442
After 2 hr., coming out of apparatus	82.4	442

Ligation of ureters was performed on a series of animals, but sudden death, presumably from cardiac arrest as has been described in the literature, was so frequent before dialyzation could be carried out that many of the animals succumbed. Finally, an interesting method of producing uremia was employed. The ureters were transplanted into the small bowel in the hope that there would be sufficient resorption of nonprotein nitrogenous bodies to produce uremia. This took place in a surprisingly short time, and high levels were reached in three or four days, associated with lethargy and diarrhea. The animals, however, maintained their intake of food and fluid, which was not the case in animals with nephrectomy of ureteral ligation.

The study showed that blood can be circulated outside the body and that with a reasonable length of dialyzing tubing moderate amounts of nonprotein nitrogen can be removed in short periods from normal and uremic animals, provided that these animals are not moribund or in a state of severe circulatory depression. The level of nonprotein nitrogen in the blood varies greatly in this state and is a less reliable

guide to the efficiency of the dialyzation than is the nonprotein nitrogen measurable in the dialysate removed during the test run (fig. 4).

It seemed obvious from the experiments as well as from the effects on patients clinically that the level of nonprotein nitrogen substances measured in the blood gave only a poor indication of the effect of such dialysis. Obviously the nonprotein nitrogen substances in the blood stream are not produced there, but are the waste products delivered to this circulating medium from the tissues in which they are produced. This circulating medium, the blood, has the function of carrying these substances to points where they are detoxified, prepared for excretion and finally carried to the kidney where they are excreted from the system. While the level of nonprotein nitrogen substances in the blood may be reduced somewhat, the essential point in treatment is to reduce

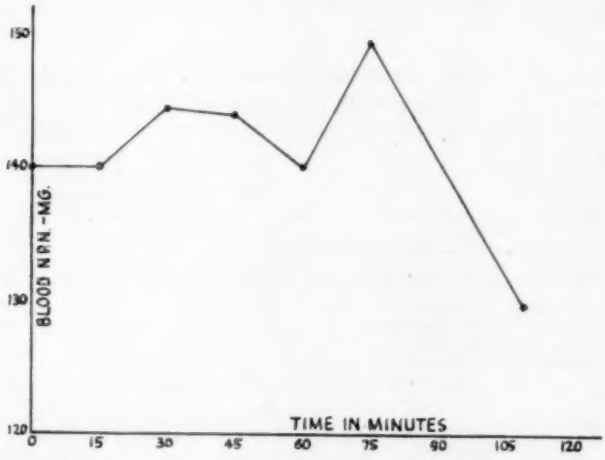

Fig. 4.—Levels of nonprotein nitrogen in dialysis over a period of almost two hours in a male dog weighing 37 pounds (16.8 Kg.), with nephrectomy (left kidney) and ligation of the right ureter. The nonprotein nitrogen recovered from the dialysate is also shown.

these and other toxic substances in the vital centers and other fixed tissues. During many of the experiments and in the clinical runs, more nonprotein nitrogen was removed than was contained in the total volume of blood in the animal, and still the level in the blood stream was lowered only slightly. It was obvious, therefore, that there is constant drainage of these substances from fixed tissues into the blood stream, one of the functions of which is to transport these substances for disposal.

It seemed of interest, therefore, to investigate this aspect of the problem. For that purpose nephrectomy was performed, and the nonprotein nitrogen of the blood and spinal fluid was followed as uremia developed in the animal. When these figures had reached a high level

in these two fluids, the animal was killed and blocks of tissue were immediately frozen and ground up, and estimations of nonprotein nitrogen were made on these by Dr. Gornall. The accompanying tables and graphs indicate the results. When the nonprotein nitrogen in the blood reached a certain level, the level in the spinal fluid was above this, and the level of the nonprotein nitrogen substances in the tissue examined was above that level again. This would tend to bear out the point already made that the blood is only a medium of collecting and washing away for disposal of these substances (figs. 5 and 6).

When, therefore, 12.97 Gm. of nonprotein nitrogen substances were removed from the patient herein reported and readings of the blood showed only a slight depression of the level of nonprotein nitrogen, it was

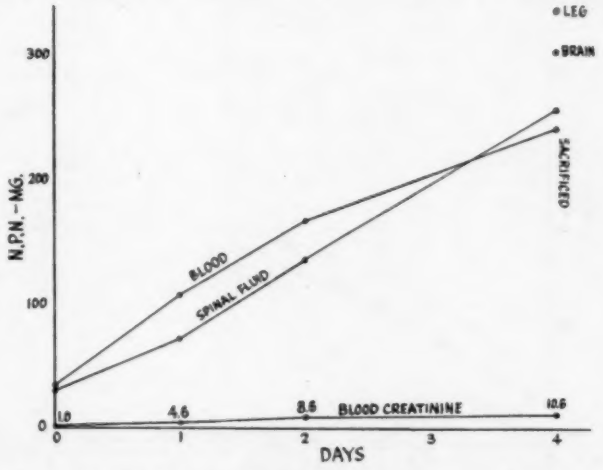

Fig. 5.—Graph showing the daily rising of nonprotein nitrogen in the blood and spinal fluid in a female dog that weighed 15 Kg. and had undergone nephrectomy (left kidney) and ligation of the right ureter. On the third day the level in the cerebrospinal fluid passed that of the blood. The animal was killed on the fourth day, and assays of tissue showed nonprotein nitrogen in leg muscle 335 mg. per hundred cubic centimeters, cardiac muscle 418 mg. and brain tissues 301 mg. The levels in the blood and cerebrospinal fluid were about 250 mg.

obvious that the removal was bringing down the level of these toxic substances in the vital fixed tissues of the patient. The proof of this was the clinical improvement of the patient, with diminishing signs of toxemia even though the nonprotein nitrogen in the blood was still at a fairly high level.

From the events observed experimentally and clinically, we think it can be assumed fairly certainly that while nonprotein nitrogen substance can be removed there are other substances also that are removed by this dialyzing system. These substances are probably responsible in large part for severe toxemia and ultimately for death. Proof of

this is the fact that in a normal animal from four to ten times the amount of urea necessary to place the nonprotein nitrogen at a high level can be given without much injurious effect. Probably, therefore, there is another substance responsible for the toxemia. This substance has not been isolated and has not been described or analyzed, but this system offers an excellent method of approach to the study of such substances, as suggested by Abel, Rountree and Turner.[2]

This work represents only early excursions into a field which offers great prospects for expansion. It might be used therapeutically in the way of removal of toxic substances as well as in the administration of substances which may be beneficial to the patient.

Several runs have been made on clinical patients to test the function of the apparatus. The clinical case which is reported is of considerable

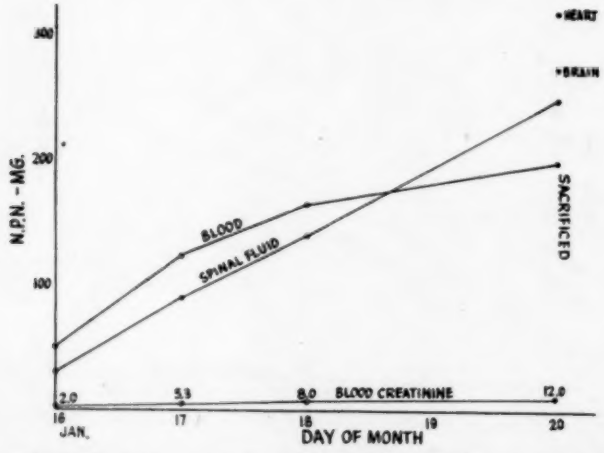

Fig. 6.—Graph showing nonprotein nitrogen levels in the blood and cerebrospinal fluid (250 mg. per hundred cubic centimeters) and in leg muscle (345 mg.), cardiac muscle (320 mg.) and brain tissue (275 mg.) following bilateral nephrectomy in a male dog that weighed 12 Kg. and had undergone nephrectomy (left kidney) and ligation of a ureter. (These are preliminary reports only.)

significance as regards the function and ability of this apparatus to perform what was intended of it.

REPORT OF A CASE

A patient, 26 years of age, following an attempt at induced abortion had anuria for nine days. During this period the patient was passing about 35 cc. of urine daily and when seen first had uremia. She was comatose, was having mild uremic convulsions, was greatly edematous and was not passing urine. She was seen by the internists, the gynecologists and the genitourologists, all of whom agreed that the case was utterly hopeless, and, in fact, they had given up treatment except for some diathermy which was being applied through the loins.

On this ninth day the patient was attached to the artificial kidney by passing a catheter through the saphenous vein into the inferior vena cava on the right

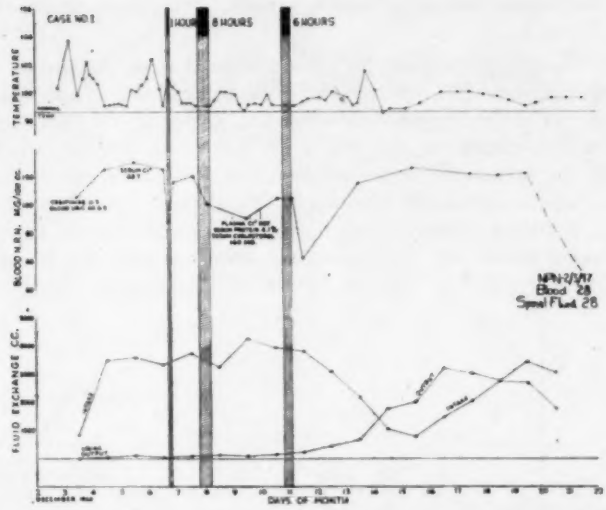

Fig. 7.—Graph from the reported clinical case, showing the clinical course preceding, during and after dialysis of the blood with the artificial kidney over a period of twenty-one days in the hospital. The shaded vertical bars on the sixth, eighth and eleventh days show the periods of dialysis with the artificial kidney over a total period of about sixteen hours. The fall to normal of the nonprotein nitrogen on Feb. 3, 1947 is indicated.

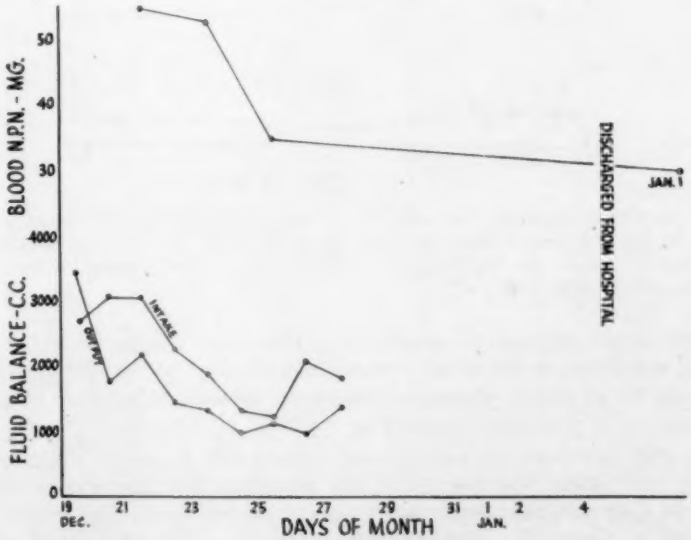

Fig. 8.—Graph (continuation of graph in figure 7) showing the later stages of recovery of the patient, with the nonprotein nitrogen back to normal and the water balance again normal.

side and another into the femoral vein on the left. With the machine running for one hour, the patient was moderately improved. The results of the run are shown in figures 7 and 8.

Toward the end of the hour the patient showed some discomfort. She experienced a fairly severe chill. Because of this, because the effects were not known and because of difficulty in following the chemical changes accurately, the dialysis was discontinued at the end of an hour (fig. 9). It was shown fairly conclusively on subsequent runs, without any similar ill effects, that probably the trouble was in inadequate washing of the tubing. On all occasions we used new tubing, including rubber tubing throughout the tambour in the pump as well as the dialyzing membrane. On subsequent occasions this was thoroughly washed with distilled water for an adequate period of time and then washed for a short

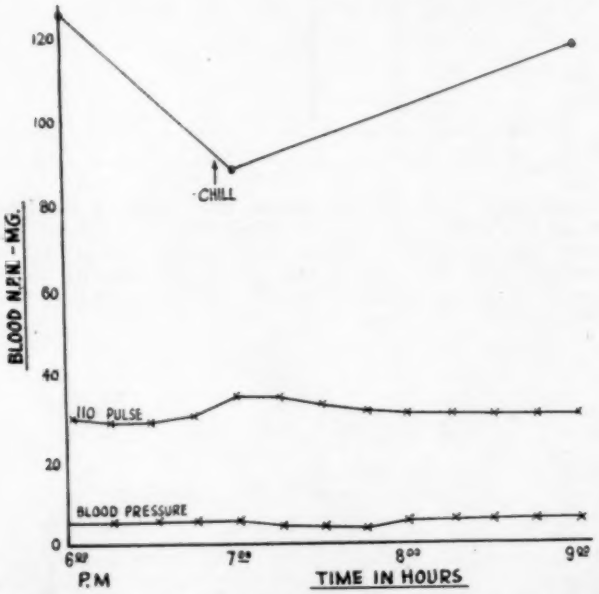

Fig. 9.—Graph showing the reduction of nonprotein nitrogen in the blood of the patient during one hour of dialysis (Dec. 6, 1946), with the removal of 330 mg. of nonprotein nitrogen in the dialysate. Thirty-three feet (about 1,006 cm.) of dialyzing tubing was used.

time with blood solution to remove any remaining substances either in the dialyzing membrane or the tubing. On subsequent runs, lasting up to eight hours, there were no ill effects whatever in the form of thermal reactions, changes in respiration, pulse rate, blood pressure or the like.

After the treatment the patient was considerably improved clinically. The next day the patient was fair. The day following that she was much worse again, and a run of eight hours was given on the machine. The results of this are shown in figure 10. The patient was greatly improved. There was still passage of only 45 cc. of urine. Three days later the patient was again seriously ill, and a run of seven hours was given, the results of which are shown in figure 11. The clinical improvement of the patient was striking. She was comatose at the beginning of each of these runs on the machine, and at the end the delirium

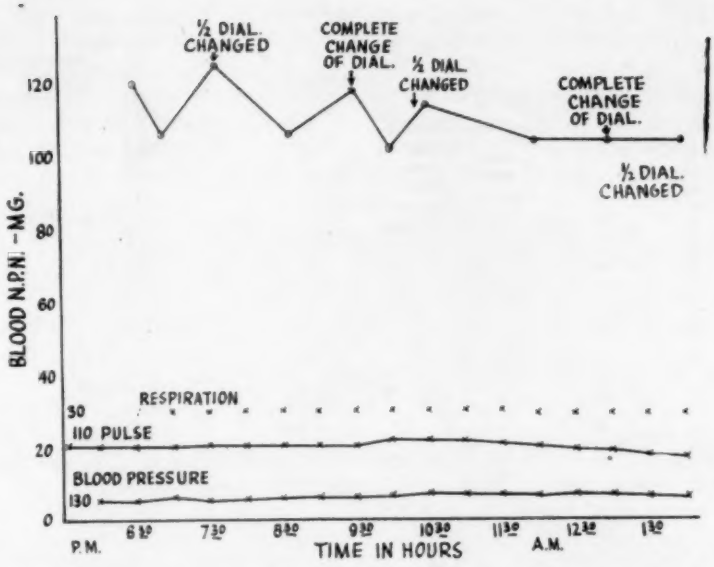

Fig. 10.—Graph showing, in the clinical patient, the second run of slightly more than eight hours (Dec. 7-Dec. 8, 1946) on the machine. The fall in the level of nonprotein nitrogen in the blood following the repeated changing of the dialysate is shown. There was no ill effect on blood pressure, pulse or respiration. There were 6,600 mg. of nonprotein nitrogen removed in the dialysate. Thirty-three feet (about 1,006 cm.) of tubing was used.

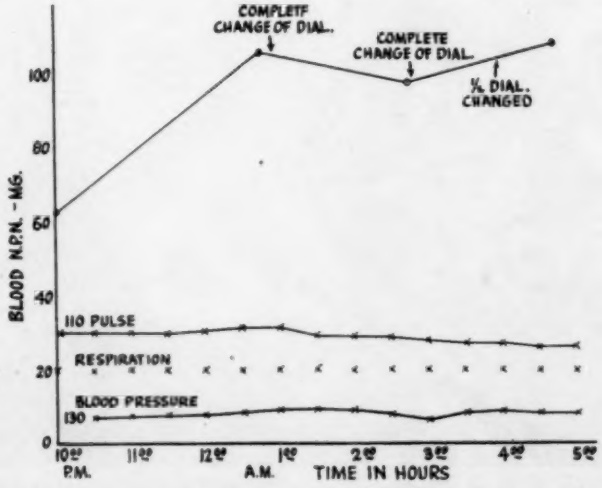

Fig. 11.—Graph showing the third run (six and one-half hours, Dec. 10-Dec. 11, 1946) on the machine. There were 6,040 mg. of nonprotein nitrogen removed from the blood during this period. Thirty-one feet (about 945 cm.) of tubing was used.

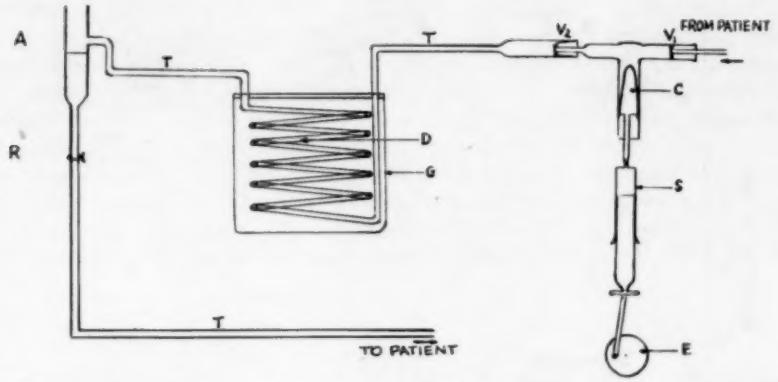

Fig. 12.—Schematic drawing of the artificial kidney (not drawn to scale). V_1 and V_2 are valves; *C* is the condum, *S* syringe, *E* eccentric, *T* rubber tubing, *A* air trap, *R* inlet control, *D* dialyzing membrane and *G* bath jar.

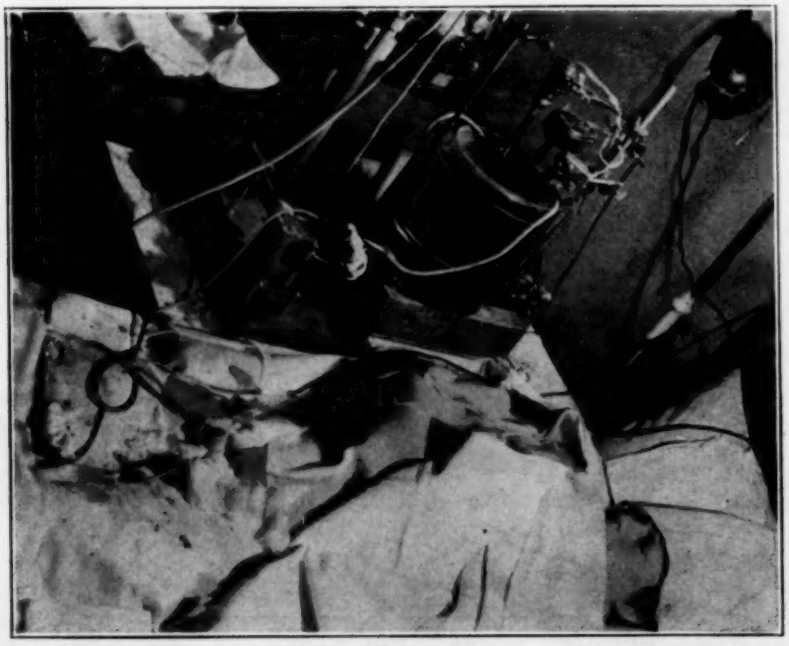

Fig. 13.—View of the patient in bed, attached to the artificial kidney.

and coma had disappeared. The patient would drink small quantities of fluid, would respond to questions and conversation and stated that she felt much better. In spite of the decided edema, she had some appearance of intelligence.

During the runs on the machine samples of blood, ascitic fluid from the peritoneal cavity and spinal fluid were removed, and determinations of nonprotein nitrogen and other substances were made from these, as indicated on the graph.

After the last dialysis there was a moderate secretion of urine, and the next day there was an enormous secretion of 4,000 cc. of urine. Subsequently the patient

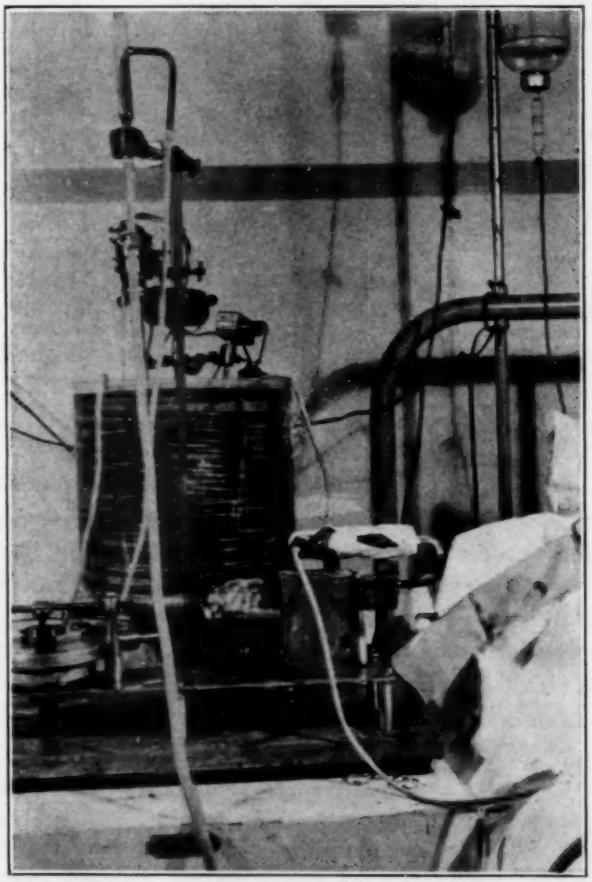

Fig. 14.—The artificial kidney in use on a patient. The glass containing the coil of dialyzing tubing, circulating pump and motor, air trap, heater of the dialysate, stirrer and thermostate are shown.

made a progressive and uninterrupted recovery, and her health returned to normal. During the next two weeks samples of blood and spinal fluid were examined, and these showed a progressive fall of nonprotein nitrogen in both blood and spinal fluid, until on the twenty-fifth day these were both normal. The edema had entirely disappeared. The patient was out of bed and going about and was in normal health. At this stage the gynecologists reported that the fetus was not present in the uterus. While there was no record of its escape, we think that one

cannot assume that the dialyzing apparatus removed it by this means. The patient was in the hospital thirty-three days.

The only remaining abnormality was a lack of concentration as shown in the two hour test. The urine otherwise was normal, and the two hour test showed a concentration only up to 1.012. However, at a later date, as shown on the final point on the chart, on the sixty-first day the nonprotein nitrogen in the blood was 28 mg. and in the spinal fluid 28 mg. per hundred cubic centimeters, and considerable improvement was demonstrated in the two hour test, as shown in table 5. Here the concentration went up to 1.018, and the diurnal and nocturnal quantities were close to normal. The patient has gone back to her regular work and is in good health.

TABLE 5.—*Results of Two Hour Concentration Test of Urine on the Sixty-First Day Following Recovery*

Time (2/3/47)	Volume, Cc.	Specific Gravity	Albumin	Sugar	Microscopic Observations
10 a. m.	120	1.012	—	—	.....
12 noon	126	1.010	—	—	.....
2 p. m.	69	1.017	—	—	.....
4 p. m.	114	1.017	—	—	.....
6 p. m.	90	7.016	—	—	.....
10 p. m.	245	1.016	—	—	.....
10 p. m. to 8 a. m.	465	1.018	—	—	Occasional white blood cells
Total	1,229*				

* Day total 764 and night total 465 cc.

SUMMARY

A report is made, after a great deal of experimental work, of an artificial kidney or dialyzing membrane which has been used in such a way that it can be applied safely to animals or to human beings. This membrane can be used to remove toxic substances from the blood. With proper buffering of the dialysate, there are no injurious effects as a result of this dialyzing process.

A clinical case of significance is described, in which a cure was effected.

Professor Van Wyke provided the patient whose record of treatment is reported, laboratory space and some chemicals were provided by Prof. Andrew Hunter, and Dr. Allan G. Gornall assisted with nonprotein nitrogen assays of tissue. Some facilities were provided by the Banting Institute. Otherwise this work was carried on with private funds only and without other assistance.

502 Medical Arts Building.

DISCUSSION

DR. VICTOIRE DARWIN LESPINASSE, Chicago: My colleagues and I are grateful to Dr. Murray for showing us a practical method of parabiosis. Experimentally, we have tried parabiosis in rats. Those that have been poisoned with mercury bichloride can be assisted over the period of acute renal damage with parabiosis. Dr. Murray's idea of tiding the patient over the period of glomerular damage is good, as borne out by our experimental work.

MEDULLARY TRACTOTOMY FOR RELIEF OF INTRACTABLE PAIN IN UPPER LEVELS

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Surgeon-in-Charge, Division of Neurological Surgery, Henry Ford Hospital
DETROIT

MEDULLARY tractotomy has already become an established procedure as a method of severing the afferent pain pathways—the spinothalamic tracts. Several surgeons deserve mention as pioneers in developing this procedure. Schwartz and O'Leary [1] reported the first case in 1941 after Sjoquist,[2] Rowbottom,[3] Walker [4] and Grant, Groff and Lewy [5] proved the method feasible from their experiences with medullary tractotomy of the descending root of the fifth cranial nerve. White [6] also reported a case in 1941, pointing out that the incision should be made caudad to the lower end of the olive. Adams and Munro [7] in 1944 reported 3 cases, in 1 of which a bilateral tractotomy was done in two stages, with survival in all. In his cases, however, the upper level of analgesia for pain was in the upper dorsal region. He apparently felt that it was not feasible to try for a higher level, because of the attending risks resulting from deeper cuts. This may be one reason that more cases have not been reported in which

Read at the fourth annual meeting of the Central Surgical Association, Chicago, Feb. 21, 1947.

1. Schwartz, H. G., and O'Leary, J. L.: Section of Spinothalamic Tract in Medulla with Observations on Pathway for Pain, Surgery **9**:183, 1941.

2. Sjoquist, O.: (*a*) Studies on Pain Conduction in the Trigeminal Nerve: A Contribution to the Surgical Treatment of Facial Pain, Acta psychiat. et neurol. (supp.) **17**:1, 1938; (*b*) Trigeminal Neuralgia: Review of Its Surgical Treatment and Some Aspects of Its Etiology, Acta chir. Scandinav. **82**:201, 1939.

3. Rowbottom, G. F.: Treatment of Pain in the Face by Intramedullary Tractotomy, Brit. M. J. **2**:1073, 1938.

4. Walker, E. A. L.: Anatomy, Physiology and Surgical Considerations of the Spinal Tract of the Trigeminal Nerve, J. Neurophysiol. **2**:234, 1939.

5. Grant, F. C.; Groff, R. A., and Lewy, F. H.: Section of the Descending Spinal Root of the Fifth Cranial Nerve, Arch. Neurol. & Psychiat. **43**:498 (March) 1940.

6. White, J. C.: Spinothalamic Tractotomy in Medulla Oblongata: Operation for Relief of Intractable Neuralgias of Occiput, Neck and Shoulder, Arch. Surg. **43**:113 (July) 1941.

7. Adams, R. D., and Munro, D.: Surgical Division of the Spinothalamic Tract in the Medulla, Surg., Gynec. & Obst. **78**:591, 1944.

there were attempts to secure an upper level of analgesia in the mid-cervical region.

Experience with this procedure has led me to believe that it is feasible to try for the upper level of analgesia, at least on one side at a time, and I report herewith 11 cases, in 9 of which unilateral section was done and in 2 of which bilateral section was done at one operation.

REPORT OF CASES

CASE 1.—A woman of 40 had intractable pain from an incurable carcinoma, with metastasis to the fifth dorsal spine on the right side. A medullary tractotomy of the left side was done Feb. 7, 1942. The operation was done under local anesthesia, with the patient in the sitting position. A suboccipital exposure on the left side was made through an inverted U-shaped incision. The cut in the side of the medulla was made about 9 mm. caudad to the obex to a depth of about 5 mm. The cut was made ventral to the bulge of the descending root of the fifth cranial nerve. There were no special technical difficulties, and the patient stood the procedure well and made a good recovery from the operation. She did have transient hemiplegia (left), which began clearing up the third day and was gone in a month. The upper level of pain algesia was between the second and third cervical segments on the right side. She died of her carcinoma four months postoperatively, having been free of her pain until death.

Comment.—I feel that the hemiplegia probably resulted from cutting a little too far caudad and causing some damage to the pyramidal fibers at the decussation.

CASE 2.—A man of 40 had abdominal pain from an incurable carcinoma of the colon. Anticipating that the pain was likely to extend upward, a bilateral medullary tractotomy was done Feb. 20, 1942. The operation was done in the sitting position under local anesthesia with a midline incision of the skin. The incisions in the medulla were made at about the level of the obex, about 5 mm. deep, with a surface cut of about 3 mm., in front of the eminence of the descending root of the fifth nerve. There was no trouble with bleeding, and the patient stood the procedure well. He moved all of his extremities, and his upper level of analgesia was at the level of the third cervical segment. However, about twelve hours postoperatively hyperthermia developed; he was unable to swallow, and there rapidly developed medullary signs, which did not respond to corrective measures. He died less than twenty-four hours after operation. Postmortem examination showed no hemorrhage and only a minimal amount of edema.

Comment.—I felt then that the cut was probably a little too far cephalad and probably a little too deep, involving the vagus nuclei.

CASE 3.—A woman of 53 had intractable pain in the left axilla from a metastatic inoperable carcinoma. A medullary tractotomy of the right side was done Oct. 9, 1942, under local anesthesia with the patient in the sitting position. The cut in the medulla was made about as in the previous case, except that it was made about 5 mm. caudad to the obex. She made a good recovery, was relieved of her pain and showed an upper pain level at the fourth cervical segment on the left. She had hemiplegia of the right side, which began clearing up by the third postoperative day and was almost gone in six days. She died at her home one month after operation from rapid pulmonary involvement by the cancer. She had been free of her pain until death.

Comment.—Here, again, I probably produced some damage to the pyramidal fibers near the decussation.

CASE 4.—A man of 40 was suffering from severe intractable pain in the right shoulder and upper extremity from an extensive recurrent sarcoma in the right shoulder. A medullary tractotomy of the left side was done on Nov. 29, 1942, under local anesthesia, and using the same technic as in the last case. There were no special technical difficulties. The patient stood the procedure well and was relieved of his pain. The upper level of analgesia to pain was at the fourth cervical segment on the right. There was no weakness of the extremities. He died five months after operation from extensive pulmonary involvement by the cancer, but had been free from pain on the right side.

CASE 5.—A woman of 43 had been suffering for about a year from constant intractable pain, associated with scarring and contractures resulting from extensive burns in the left axilla and upper extremity. Inasmuch as the pain persisted in spite of all procedures, I finally advised medullary tractotomy, although there was a strong associated psychoneurotic problem. The procedure was done on the right side, with the same technic as in the 2 previous cases. No paralysis resulted, and it appeared that she was relieved of the pain in her arm and shoulder, but later variable pains developed in other parts of her body which were not related to the medullary section and were psychoneurotic in origin.

CASE 6.—A woman aged 66 was suffering from intractable pain in the right shoulder and arm from a metastatic inoperable carcinoma. A medullary tractotomy of the left side was done on Dec. 22, 1944, using the same technic as in the previous 3 cases. The patient stood the procedure well and was relieved of her pain until her death at home months later. She showed a transient homolateral weakness for a few days, but she was grateful for her relief of pain.

CASE 7.—A woman of 44 had been suffering from intractable pain in the left arm and shoulder from inoperable carcinoma. A medullary tractotomy of the right side was done June 15, 1945, using the same technic as with the others. The results were excellent, and the pain level obtained was at the third cervical segment on the left. No motor impairment resulted. She was freed of her former pain until her death two months later from extensive local and pulmonary involvement.

CASE 8.—A man of 60 was suffering from intractable pain of his left arm and shoulder from a destructive lesion of the upper dorsal aspect of the spine and right scapula. A medullary tractotomy of the left side was done Sept. 10, 1945. He stood the procedure well and has remained free of his former pain. The level for analgesia was at the fourth cervical segment. There was a transient homolateral weakness, which began clearing up in ten days and disappeared within a month. He is still alive and able to be about. He has taken trips to Mexico and Europe since the operation. The lesion slowly increased in extent for a while, and he had some pain in the left shoulder, but later that disappeared. The final diagnosis of the destructive lesion is uncertain.

CASE 9.—A woman of 60 had pain in the high dorsal region from an incurable malignant growth. A medullary tractotomy of the right side was done, the same as in previous cases, on Feb. 2, 1946. The patient stood the procedure well, and an upper level of analgesia was obtained at the third cervical segment on the right. A transient homolateral weakness was present for a few days. She remained free of her former pain until her death two months later.

CASE 10.—A man of 40 was suffering from intractable pain in the left side of the high dorsal region from an incurable malignant growth. A medullary

tractotomy of the right side was done, the same as in previous cases. The patient stood the procedure well and was relieved of his former pain. He moved all of his extremities well after the operation, and the upper level for pain was at the third cervical segment on the left side. He died two days postoperatively from a slowly developing hemorrhage, which was recognized too late to save his life.

Case 11.—A woman of 51 years was suffering from bilateral intractable pain from an incurable malignant growth. A bilateral medullary tractotomy was done, because I felt that such an operation, done at one sitting, was a feasible procedure. This operation was done on Feb. 5, 1947, in the sitting position and under local anesthesia augmented with sodium pentothal administered intravenously. Because of the latter, the patient did not respond satisfactorily at the time of sensory stimulation, and I cut about as in previous cases, possibly a little more extensively to insure the incision's being deep enough. She stood the procedure well, was able to move all her extremities, talked and swallowed fairly well and had a pain level bilaterally at the second cervical segment. She seemed to be getting along satisfactorily during the first postoperative day, but then there rapidly developed medullary signs which were interpreted as edema. Respiratory failure supervened late on the second postoperative day. She improved when put in the respirator, but died on the seventh postoperative day, with signs of terminal pneumonia. No postmortem examination could be made.

Comment.—It is unfortunate that I was not able to determine whether death came as a result of hemorrhage or secondary degenerative changes from the sections. However, this case demonstrated that a bilateral section is not immediately incompatible with life. From experimental studies, not yet published, it would appear that such a procedure is feasible. But it is probable that with bilateral section there is not the margin of safety as with unilateral section. It is probable that I might have been able to cut a little less deeply had she been able to respond more accurately during the cutting.

As to technic, the operations were all done under local anesthesia with the patients sitting up in the neurosurgical chair. With the one-sided cutting a unilateral inverted U-shaped incision was used, cutting away the arch of the atlas and enlarging the foramen magnum on that side. Exposure of the side of the medulla up to the level of the inferior olive and obex was accomplished with a little elevation of the lower pole of the cerebellum. The vertebral artery was covered with a thin strip of "cottonoid." Cotton stamps soaked with procaine hydrochloride, 1 per cent solution, were held against the medulla, and then the fine hairlike vessels which interfered with exposure were shrunk away with electrocautery. The level of incision into the medulla was determined by the fine rootlets of the tenth and eleventh nerves. The cuts were made caudad to the last of the vagus rootlets and cephalad to the last of the spinal rootlet of the eleventh nerve. It is shown on the diagram of the right side of the medulla (fig. 1). It was a point about 5 to 6 mm. caudad to the obex.

The cutting was done with a small right-angled blade on a long handle set at a 30 degree angle to the coronal plane. This permitted making a small surface cut 2 to 3 mm. long. The cutting blade is 4.5 mm. long. After the blade had been plunged in once, there was usually no further remonstrance by the patient and he could be tested with a

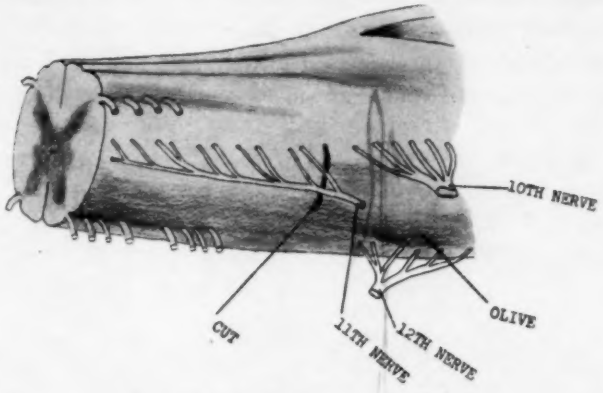

Fig. 1.—Right side view of the medulla oblongata.

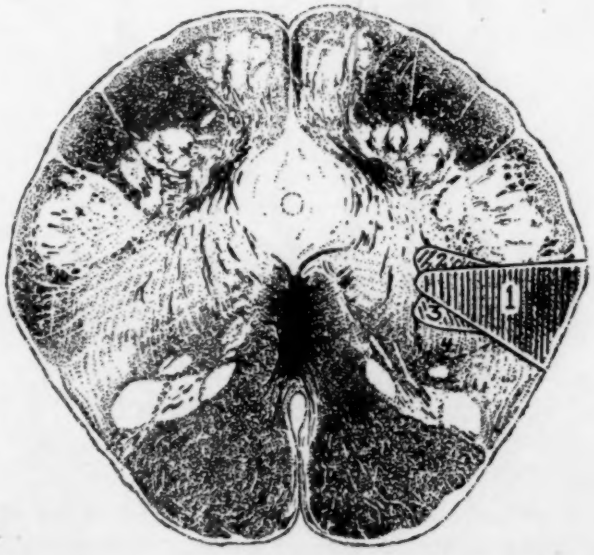

Fig. 2.—Transverse section of the medulla oblongata at the lower end of the olive.

pin for the upper level of analgesia. If the level was not high enough after this first section (fig. 2 [*1*]), further cuts were made as shown in figure 2 (*2* and *3* of the stippled areas), or if a lower level was desired the cuts were made as shown in figure 2 (*4*). I have most

recently done the secondary cutting (fig. 2 [*2* and *3*] with the blades which are made as hooks (fig. 3 [*1* and *6*]). These permit undercutting without so much surface cutting.

There has never been any bleeding from the cutting, except from the minute hairlike vessels on the surface. With the blade of the knife one can usually dodge the branches of the posterior cerebellar artery without disturbing them.

The dura has always been closed loosely and not made water tight, and one must be careful to obtain absolute hemostasis during closure.

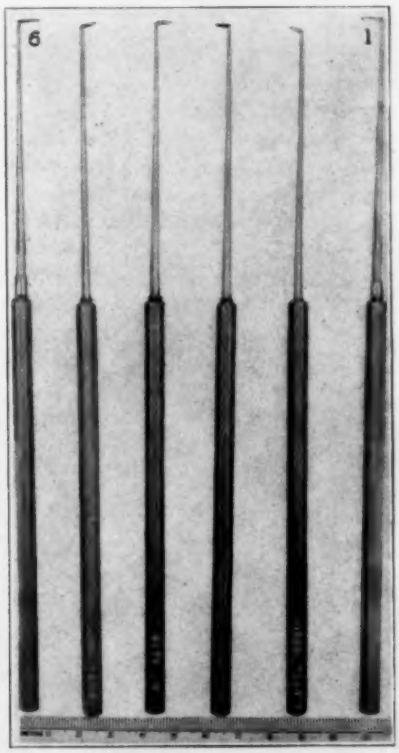

Fig. 3.—Cutting instruments used.

The danger of air embolism must be borne in mind as one of the risks of operating in the sitting position. Postoperative bleeding is possibly more likely to occur after this upright approach and probably accounted for 1 or 2 of the 3 deaths.

The patients have stood this surgical procedure surprisingly well, considering that they were victims of cancer. I have used no special type of head dressing afterward, and they were encouraged to move frequently from side to side.

SUMMARY

Nine cases of unilateral and 2 cases of bilateral medullary tractotomy done for intractable pain in the upper part of the torso are reported. All of them resulted in a high level of pain algesia. The 2 patients in whom bilateral medullary tractotomy was done, and 1 in whom unilateral medullary tractotomy was done, died, 1 or 2 of these probably from hemorrhage. There was transient homolateral paralysis in 5 cases. I feel that this can be avoided by cutting only in the areas which are shown stippled in the diagram (fig. 3) and at the proper site for section (fig. 1) and by avoiding postoperative hemorrhage.

I report these cases mainly to show that the procedure is feasible and with the hope that it will stimulate others to use it to relieve patients with intractable pain of the shoulders and lower cervical regions. With further experience it is believed that bilateral section at one sitting may also be feasible.

ACUTE APPENDICITIS

An Analysis of Eight Hundred and Seventy-Eight Cases at St. Luke's Hospital, Chicago

E. LEE STROHL, M.D.
AND
FRANCIS E. SARVER, M.D.
CHICAGO

APPENDICITIS, as a clinical entity, has been recognized since 1886, when Fitz,[1] of Boston, coordinated the theories of inflammatory disease in and about the cecum. He originated the term "appendicitis" and described the clinical picture, placing particular emphasis on its early diagnosis and treatment. Among the pioneers in the development of the technic for the removal of the appendix were Sands, listed by Ficarra,[2] McBurney,[3] McArthur [4] and Murphy.[5] Sands was among the first to attempt drainage of an appendical abscess. McBurney, in 1894, reported the technic of the muscle-splitting incision, advocating its use exclusively for nonsuppurative, chronic or interval appendicitis. McArthur had then been using the same incision for over three years. McArthur advocated its use in all types of appendicitis, including fulminating types of appendical infection. The mortality rate resulting from acute appendicitis prior to the adoption of chemotherapeutic measures was reported by various authors as 4.5 to 5 per cent. Approximately two thirds of all deaths resulting from peritonitis in the United States

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Read at the fourth annual meeting of the Central Surgical Association Feb. 21, 1947, Chicago.

From the Departments of Surgery, St. Luke's Hospital and the University of Illinois College of Medicine.

1. Fitz, R. H.: Perforating Inflammation of the Vermiform Appendix, with Special Reference to Its early Diagnosis and Treatment Also, Tr. A. Am. Physicians **1**:107-144 (June) 1886.

2. Ficarra, B. J.: American Pioneers in Abdominal Surgery, Am. J. Surg. **64**:282-286 (Feb.) 1944.

3. McBurney, C.: The Incision Made in the Abdominal Wall in Cases of Appendicitis, with a Description of a New Method of Operating, Ann. Surg. **20**: 38-43 (Aug.) 1894.

4. McArthur L. L.: Choice of Incisions of Abdominal Wall, Especially for Appendicitis, Chicago M. Recorder **7**:289-292 (Nov.) 1894.

5. Murphy, J. B.: Appendicitis, with Original Report, Histories and Analysis of One Hundred and Forty-One Laparotomies for that Disease Under Personal Observation, J. A. M. A. **22**:302-308 (March 3) 1894.

followed acute appendicitis with perforation at that time. The overall mortality rate in acute appendicitis is on the decline. However, the mortality rate in cases of acute appendicitis with perforation has shown no great improvement. This mortality rate is reported as 5 to 17 per cent. These factors have prompted a further analysis of acute appendicitis at St. Luke's Hospital as well as the factors contributing to death from acute appendicitis.

FACTORS IN THIS STUDY

This study represents a series of 878 consecutive and unselected cases of acute appendicitis occurring at St. Luke's Hospital during the period 1939 through 1945. The patients were residents of the Chicago area and represent a cross section of the patients seen in this community. The patients included in this series were all operated on, and the appendix was observed to be acutely inflamed or the source of an abscess. In each instance microscopic confirmation of appendical disease was reported by the pathologist. Cases in which the disease was reported by the surgeon and the pathologist as "subacute," "chronic," "interval" or "chronic mechanical" are not included in this report. The previously reported series over the period 1932 to 1939 by one of us (E. Lee Strohl) from St. Luke's Hospital [6] will be compared with this series.

Each case analyzed has been placed in one of three groups: (1) acute appendicitis without rupture, a condition in which there was no localized pus or perforation present at the time of operation and the inflammatory process was confined to the appendix. (2) acute appendicitis with perforation, a condition in which the appendix was described by the surgeon and the pathologist as perforated and localized or diffuse peritonitis was present at the time of operation. (3) appendical abscess, in which a well localized area of pus was observed at the time of operation. We believe that the terms spreading peritonitis, diffusing peritonitis and local peritonitis are confusing as criteria for a statistical survey of this type. These terms may be inaccurate, since it is difficult at operation to determine the extent of peritonitis in any given case without abdominal exploration. Exploration is not justified in the presence of acute appendicitis. One disadvantage to the use of these three main groups is that, occasionally, cases of severe appendicitis with gangrene and peritonitis will fall in the "acute unruptured" group, because no gross or microscopic evidence of perforation was noted. Peritoneal culture as a criterion of spread of infection beyond the appendix was not used, because the culture had not been obtained in each instance.

6. Strohl, E. L.: Acute Appendicitis: Analysis of the Records of Three Hundred Cases, Illinois M. J. **74**:171 (Aug.) 1938.

ANALYSIS OF CASES

Age.—Two hundred and twenty-four cases occurring in the second decade of life was the greatest number occurring in any age group (table 1), while there were 222 cases in the third decade and 149 in the fourth decade. Thus, in the second, third and fourth decades there were 599, or 67.8 per cent, of the total series. The average age of all patients included in this series was 28.5 years. The greatest number of perforated appendixes also occurred in the second, third and fourth decades (53, or 55 per cent, of all cases with perforation).

It is interesting to note in our series the similarity in the pattern of the disease in children under 5 years of age and in patients over 70 years of age. Of 22 cases in children under 5 years of age there were 5 with perforation and 2 with abscesses, whereas in 18 cases in patients past 70 years of age there were 6 with perforation and 4 with abscesses.

TABLE 1.—*Age Incidence*

Pathologic Condition	0-5 Yr.	5-10 Yr.	10-20 Yr.	20-30 Yr.	30-40 Yr.	40-50 Yr.	50-60 Yr.	60-70 Yr.	Over 70
Acute appendicitis without rupture	15	52	207	202	118	80	34	9	8
Acute appendicitis with perforation	5	5	12	14	19	20	10	6	6
Appendical abscess	2	3	5	6	12	10	7	7	4
Total	22	60	224	222	149	110	51	22	18

TABLE 2.—*Sex Distribution*

Sex	0-5 Yr.	5-10 Yr.	10-20 Yr.	20-30 Yr.	30-40 Yr.	40-50 Yr.	50-60 Yr.	60-70 Yr.	Over 70	Total
Male	14	38	102	107	83	70	38	12	10	474
Female	8	22	122	115	66	40	13	10	8	404

Sex.—In this series there was only a slight predominance in the number of cases occurring in male patients. Of 878 patients, 474 (54 per cent) were male and 404 (46 per cent) were female (table 2). (This study was made during war years.)

Classification.—The number of cases of acute appendicitis without rupture was 725, or 82.6 per cent (table 3). The number of cases of acute appendicitis with perforation was 97, or 11 per cent. In 56 cases, or 6.4 per cent, an abscess was observed at operation.

Mortality.—During the period of 1932 to 1937, 9 deaths in 300 consecutive cases, a mortality rate of 3 per cent, were reported from St. Luke's Hospital.[6] During the period 1937 to 1939, there were 10 deaths in 519 cases, a mortality rate of 1.92 per cent, reported from St. Luke's hospital.[7]

7. Strohl, E. L.: Appendectomy by the Muscle-Splitting Technic, S. Clin. North America **22**:1-8 (Feb.) 1942.

There were 13 deaths, following surgical intervention, in the present series of 878 cases. This represents an over-all mortality rate of 1.48 per cent. All deaths occurring after operation for acute appendicitis are included in this study. Two of these deaths occurred from apparent extra-abdominal causes and are included in the 13 deaths (table 4).

There were 4 deaths following the removal of an unruptured appendix in the acute stage of inflammation, a mortality rate of 0.55 per cent. As would be expected in the group with acute appendicitis in which there was perforation, there were 8 deaths in 97 cases, a mortality rate of 8.25 per cent. This was the highest mortality rate of any of the three groups. There was 1 death in the 56 cases of appendical abscess, a mortality rate of 1.78 per cent.

TABLE 3.—*Classification*

Pathologic Condition	Number of Cases	Percentage
Acute appendicitis without rupture	725	82.6
Acute appendicitis with perforation	97	11.0
Appendical abscess	56	6.4
Total	878	100.0

TABLE 4.—*Mortality*

Pathologic Condition	Number of Cases	Number of Deaths	Mortality Percentage 1939 Through 1945
Acute appendicitis without rupture	725	4	0.55
Acute appendicitis with perforation	97	8	8.25
Appendical abscess	56	1	1.78
Total	878	13	1.48

Analysis of Deaths.—The youngest patient that died was 2 years of age, and the oldest was 80 years of age. Eight of the deaths occurred in the fifth and sixth decades, the average age being 42.3 years. Four deaths occurred after removal of an unruptured appendix with acute inflammation. In 2 of this group generalized peritonitis developed, as observed at autopsy. One of the patients was an 80 year old diabetic person, who died of a massive pulmonary embolus ninety-six hours after operation. Autopsy revealed the peritoneum to be free of infection. The remaining death in the group in which the appendix was unruptured was that of a 49 year old man, who died suddenly twelve hours after operation. The cause of death was undetermined.

In the group with acute appendicitis with perforation there were 8 deaths. The patients ranged in age from 3 to 58 years. All deaths

were attributed directly to generalized peritonitis with paralytic ileus, and in 1 instance there was concomitant uremia. Five of the 8 patients in this group had taken a cathartic or an enema shortly after the onset of their abdominal symptoms. Two of this group had purged themselves with both magnesium sulfate and enemas.

The single death in the group with appendical abscess was that of a boy of 2 years. Symptoms were present for two weeks prior to admis-

TABLE 5.—*Causes of Death*

Case No.	Sex	Age	Type of Pathologic Condition	Duration of Symptoms	Treatment with Sulfonamide Drugs	Drain Used	Cause of Death	Catharsis Used	Autopsy
1	M	40	Acute appendicitis without rupture	24 hr.	Yes	Yes	Generalized peritonitis	Enema	Yes
2	F	80	Acute appendicitis without rupture	72 hr.	Yes	No	Pulmonary embolus	None	Yes
3	M	29	Acute appendicitis without rupture	24 hr.	None	No	Generalized peritonitis	None	Yes
4	M	49	Acute appendicitis without rupture	48 hr.	None	No	Undetermined 12 hr. after operation	None	No
5	M	56	Acute appendicitis with perforation	36 hr.	None	Yes	Generalized peritonitis	Saline laxative	No
6	M	49	Acute appendicitis with perforation	48 hr.	Yes	Yes	Generalized peritonitis	Magnesia magma	No
7	F	27	Acute appendicitis with perforation	36 hr.	None	No	Generalized peritonitis	Magnesium sulfate, enema	No
8	M	53	Acute appendicitis with perforation	48 hr.	None	Yes	Generalized peritonitis	Magnesium sulfate, enema	Yes
9	M	58	Acute appendicitis with perforation	48 hr.	Yes	Yes	Generalized peritonitis	None	Yes
10	M	56	Acute appendicitis with perforation	48 hr.	Yes	Yes	Generalized peritonitis	None	No
11	F	3	Acute appendicitis with perforation	24 hr.	Yes	Yes	Generalized peritonitis	None	No
12	M	49	Acute appendicitis with perforation	28 hr.	Yes	Yes	Generalized peritonitis	Castor oil	No
13	M	2	Appendical abscess	2 wk.	Yes	Yes	Generalized peritonitis	Magnesia magma repeatedly	No

sion to the hospital, and the child was dehydrated and septic. A mass was palpable in the right lower quadrant of the abdomen. At operation an abscess was drained, without attempt at appendectomy, since the appendix was not easily accessible. The patient died eight hours after operation.

Duration of Symptoms.—The duration of symptoms was determined from the onset of symptoms until admission to the hospital. The period of time that had elapsed prior to admission varied in this group of deaths from twenty-four hours to two weeks. The average elapsed time prior to

hospitalization was sixty-seven hours. This compares closely with the elapsed time in the cases reported by Reid and Montanus [8] from the Cincinnati General Hospital, in which there was a delay in hospitalization of sixty-four and nine-tenths hours.

Chemotherapy.—Sulfonamide drugs were used intraperitoneally and parenterally in the majority of the cases of acute appendicitis with perforation and in appendical abscess since the latter part of 1940 at St. Luke's Hospital. It would appear that the sulfonamide drugs were helpful in reducing the morbidity, although there has been no decided reduction of mortality indicated by comparison of present figures at St. Luke's Hospital with those of the period prior to use of sulfonamide drugs. Statistically, the effect of sulfonamide drugs would be shown only in the over-all mortality rate, inasmuch as there was no control series. Analysis of the deaths reveals that the sulfonamide drugs were used, in dosages considered adequate, in 7 of the 13 fatalities. These

TABLE 6.—*Yearly Mortality*

Year	Number of Cases	Deaths	Percentage Mortality
1939	144	3	2.0
1940	141	2	1.4
1941	128	2	1.5
1942	130	3	1.5
1943	109	1	0.9
1944	110	2	1.8
1945	116	0	0

figures, however, fail to reflect the number of cases of severe peritonitis in which there was recovery and in which the drug was undoubtedly effective.

The mortality rates for each year are listed in table 6, showing a 2 per cent mortality in 1939 which decreased to 0.9 per cent in 1943 and increased to 1.8 per cent in 1944. During 1945, there were no deaths in 116 cases in which there was surgical treatment at St. Luke's Hospital. Antibiotic drugs were not used in this series of cases.

Aycock and Farris [9] reported a substantial decrease in mortality rate, from 5.2 per cent over a four year period when sulfonamide drugs were not used to 1.2 per cent during the period 1940 to 1944 when the sulfonamide drugs were employed. In the cases of acute appendicitis with perforation the mortality rate was reduced from 31 per cent to 10.4 per cent concomitant with chemotherapy.

8. Reid, M. R., and Montanus, W. P.: Appendicitis: An Analysis of 1,153 Cases at the Cincinnati General Hospital, J. A. M. A. **114**:1307-1311 (April 6) 1940.

9. Aycock, T. B., and Farris, E. M.: Appendicitis: The Possible Effects of Sulfonamide on Mortality, Ann. Surg. **121**:710-717 (May) 1945.

Incision.—The McBurney-McArthur incision was used almost without exception in this series of cases. In the few instances in which other incisions were employed the choice of another incision was made because the diagnosis was in error or indefinite.

TABLE 7.—*Reported Mortality Rates*

Author Reporting	Acute Appendicitis Without Rupture		Acute Appendicitis With Perforation		Appendical Abscess		Total	
	Number of Cases	Mortality Percentage	Number of Cases	Mortality Percentage	Number of Cases	Mortality Percentage	Number of Cases	Mortality Percentage
Reid and Montanus,[8] Cincinnati General Hospital (1934 to 1938)	583	1.0	209	17.2	129	10.0	921	6.0
Green and Watkins,[10] Cleveland City Hospitals (1930 to 1941)	14,605	0.94	3,216	18.6	1,550	12.6	19,309	4.8
Cutler and Hoerr,[11] Peter Bent Brigham Hospital (1913 to 1941)	1,604	1.2	339	17.1	247	7.3	2,192	4.4
Stafford and Sprong,[12] Johns Hopkins Hospital (1931 to 1939)	838	0	196	14.2	283	7.1	1,317	3.6

TABLE 8.—*Reported Mortality with Use of Sulfonamide Drugs*

Author Reporting	Acute Appendicitis Without Rupture		Acute Appendicitis With Perforation		Appendical Abscess		Total	
	Number of Cases	Mortality Percentage	Number of Cases	Mortality Percentage	Number of Cases	Mortality Percentage	Number of Cases	Mortality Percentage
Aycock and Farris,[9] Baltimore City Hospital (1940 to 1944)	418	0	55	5.7	27	3.0	300	1.2
Mueller,[13] Roosevelt Hospital, New York (1940 to 1944)	573	0	110	0.91	56	3.57	739	0.40
St. Luke's Hospital, Chicago (1939 to 1945)	725	0.55	97	8.25	56	1.78	878	1.48

Comment.—There has been slight improvement in the over-all mortality rate for this seven year series, as compared with the previously analyzed seven year series. The improvement is not as great as some authors have reported since the advent of chemotherapy.

Prior to the general use of chemotherapy, Reid and Montanus [8] reported an over-all mortality rate of 6.0 per cent (1934 to 1938), Green

and Watkin [10] 4.8 per cent (1930 to 1941), Cutler and Hoerr [11] 4.4 per cent (1913 to 1941) and Stafford and Sprong [12] 3.6 per cent (1931 to 1939). Authors reporting since the sulfonamide drugs have been generally used, list somewhat lower mortality rates: Aycock and Farris [9] 1.2 per cent (1940 to 1944), and Mueller [13] 0.40 per cent (1940 to 1944). Stafford and his co-workers [14] in 145 cases of appendical peritonitis in 1942 reported a mortality of 3.4 per cent (table 8).

SUMMARY AND CONCLUSIONS

In a series of 878 cases of acute appendicitis at St. Luke's Hospital during 1939 to 1945, 725 were without rupture, 97 were accompanied with perforation and peritonitis and in 56 abscesses had formed. Criteria are given for the classification of acute appendicitis without rupture, acute appendicitis with perforation and appendical abscess. Stress is laid on the importance of pathologic examination of the appendix in order to obtain accurate statistics.

The over-all mortality rate of 1.48 per cent is broken down as follows: 0.55 per cent in acute appendicitis without rupture, 8.25 per cent in acute appendicitis with perforation and 1.78 per cent in appendical abscess. An analysis of the deaths revealed that 11, of a total of 13 patients, died as a direct result of progression of the appendical infection or of specific complications. One patient died of pulmonary embolism. The cause of 1 death was undetermined. Delay in operation continued as a major factor in death in the cases of acute disease with perforation, and the average elapsed time from onset of symptoms until admission to the hospital was sixty-seven hours. The over-all mortality rate of 1.48 per cent at this time, as compared with 1.92 per cent in 1939, reflects little or no evidence that the sulfonamide drugs have been a significant factor in the reduction of mortality in acute appendicitis at St. Luke's Hospital.

122 S. Michigan Avenue.

10. Green H. W., and Watkins, R. M.: Appendicitis in Cleveland, Surg., Gynec. & Obst. **83**:5-613-624 (Nov.) 1946.

11. Cutler, E. C., and Hoerr, S. O.: Acute Appendicitis: A Twenty-Five Year Study, J. Michigan M. Soc. **41**:203-210 (March) 1942. Hoerr, S. O.: Mortality Factors in Acute Appendicitis, Surgery **18**:305-317 (Sept.) 1945.

12. Stafford, E. S., and Sprong, D. H., Jr.: Mortality from Acute Appendicitis in Johns Hopkins Hospital, J. A. M. A. **115**:1242-1245 (Oct. 12) 1940.

13. Mueller, R. S.: The Local Use of Sulfonamide in the Treatment of Acute Appendicitis, Ann. Surg. **122**:625-630 (Oct.) 1945.

14. Stafford, C. E.; Besevick, J., and Deeb, P. H.: Evaluation of the Sulfonamides in Treatment of Peritonitis of Appendical Origin, Am. J. Surg. **64**:227-234 (May) 1944.

DISCUSSION

Dr. Otto W. Niemeier, Hamilton, Ontario, Canada: I would like to compliment Dr. Strohl on his excellent paper on appendicitis. I feel that this subject warrants a few minutes of discussion. He does not present as remarkable a drop in mortality as is shown in some sections. A more progressive drop has occurred in the Hamilton General Hospital, from 5 per cent to 4 per cent and finally to 0.5 per cent. I was interested to know that it rose in Dr. Strohl's series from 0.9 to 1.48 per cent, which is not a remarkable rise but bears out something that I believe is occurring. I believe that this remarkable improvement has led to a feeling of complacency on the part of the public and perhaps the medical profession in regard to acute appendicitis. I have the impression that more cases with perforation and cases of late disease with prolonged morbidity are being seen. The necessity for early operation in this condition should continue to be stressed.

In regard to the reduction in mortality, I believe that there are other factors as important as chemotherapy. I believe that suction drainage has been used more lately, and to that I attribute a considerable improvement in the hands of surgeons. I think that in postgraduate teaching one should impress students with the necessity for early operation in acute appendicitis in spite of these weapons which make it seem so safe.

EXPERIENCES WITH THE BLALOCK OPERATION FOR TETRALOGY OF FALLOT

F. D. DODRILL, M.D.
DETROIT

THE BLALOCK operation [1] is the anastomosis of one of the systemic arteries arising from the aortic arch to either the right or the left pulmonary artery. This may be done by either an end to side or an end to end method of suture. The operation is indicated in cases of congenital pulmonary stenosis or atresia of the pulmonary orifice.

Although pure pulmonary stenosis does occur, most children with this anomaly also have the associated defects of dextroposition of the aorta, interventricular septal defect and right ventricular enlargement. This is known as tetralogy of Fallot. The disabling factor in the malformation is the pulmonary stenosis, which prevents sufficient blood from reaching the lungs to permit normal oxygenation of the blood.

The diagnosis of pulmonary stenosis is made on the presence of noticeable cyanosis, clubbing of the fingers and toes, increased red blood cell count and the appearance of the heart in roentgenologic and fluoroscopic examination. Great emphasis is placed on the fluoroscopic examination, there being greatly diminished or absence of pulsations of the pulmonary arteries at the hilus of the lung. A systolic murmur, heard best at the level of the second or third anterior interspace to the left of the sternum, may or may not be present. The heart is not enlarged except during the terminal stages of the disease when some increase in its size may take place.

Thirteen operations have been performed. This includes all cases in which an incision was made. One patient was operated on the second time, there being 12 patients in this group. In all cases the diagnosis was confirmed by the observation of a small pulseless or nearly pulseless pulmonary artery. In 1 patient no pulmonary artery was present, there being a network of small collateral arteries about the pulmonary hilus, which probably arose from the bronchial artery. An anastomosis was, of course, not performed in this patient.

Read at the fourth annual meeting of the Central Surgical Association, Chicago, Feb. 21, 1947.

1. Blalock, A., and Taussig, H. B.: Surgical Treatment of Malformations of the Heart in Which There Is Pulmonary Stenosis on Pulmonary Atresia, **128**:189 (May 19) 1945. Blalock, A.: Ann. Surg. **124**:879 (Nov.) 1946.

A curved inframammillary incision was made in all cases, the third anterior interspace being entered. Either the right or the left pleural space was entered, depending on the position of the aortic arch. In this malformation the aortic arch may be on either the right or the left side. An approach was made opposite to the side on which the arch was present. The position of the arch was determined by fluoroscopy of the chest as well as by the administration of barium by mouth in order to determine which side of the esophagus was indented by it, the left arch indenting the left side and the right arch indenting the right side of the esophagus in the anterioposterior view.

All patients have been operated on with an experienced anesthetist administering the anesthetic agent. Cyclopropane has been used in all cases with an endotracheal tube in place. The respiratory act has

TABLE 1.—*Age, Sex, Systemic Vessel Used and the Clinical Result*

Case No.	Patient	Age, Yr.	Sex	Systemic Vessel Used	Result
1	N. J.	9	M	Left common carotid	Excellent
2	C. H.	5	M	Left common carotid	Excellent
3	P. S.	12	F	Left common carotid	Died
4	R. D.	4½	M	Right common carotid	Excellent
5	P. P.	7	M	(No anastomosis)	No change
6	P. P.	7	M	(No anastomosis)	No change
7	D. B.	11	M	Right subclavian	Excellent *
8	P. H.	5	M	No anastomosis	Died
9	P. C.	5	F	Right common carotid	Excellent
10	A. S.	4	F	Right subclavian (end to end)	Died
11	L. G.	12	F	Left subclavian	Fair
12	W. Z.	3½	M	Right subclavian (end to end)	Good
13	C. M.	3½	M	Right subclavian	Not yet determined (operation only recent)

* Cerebral thrombosis developed in this patient, but he recovered.

been entirely controlled or, at least, assisted. This method has permitted the operation to be performed in a comparatively quiet field. One patient in this group, however, was in such precarious condition that the lung could not be permitted to collapse without serious respiratory difficulty. It was kept almost fully inflated, and the field of operation was packed off to permit the operation to be completed. The technic of anastomosis which has been described by Dr. Blalock has been used, except in a few cases in which the pulmonary artery was so small and, therefore, the incision in it so small, that interrupted sutures instead of a continuous suture were used.

Table 1 shows the systemic artery used. In 5 patients the common carotid artery was used for the anastomosis, and in the remaining patients the subclavian artery was used. The innominate artery has not been used in any patient. When an artery the size of the innominate was desired, it was thought to be too short to reach to the pulmonary

artery. Therefore, the subclavian artery was ligated and divided near its origin, and sufficient length of the common carotid was developed so as to reach to the point of anastomosis. By such a method the full volume of blood passing through the innominate artery reaches the lungs. An end to end method of suture was used in 2 patients, the remaining anastomoses being carried out by the end to side technic.

The clinical results are also shown in table 1. By an excellent result is meant that the cyanosis disappeared, the red blood cell count became decidedly decreased, the clubbing of the fingers and toes receded or disappeared and the physical reserve of the patient was greatly improved. The arterial oxygen saturation has increased in all patients who survived the operation. One patient was unusual in this respect. The patient in case 9 showed an arterial oxygen saturation of 27.0 volumes per cent before the common carotid was anastomosed to the right pulmonary artery. Two weeks following this procedure the arterial

TABLE 2.—*List of Fatal Cases, Showing the Vessel Used, the Red Blood Cell Count, the Hematocrit Reading and the Cause of Death*

Case No.	Systemic Artery Used	Red Blood Cell Count	Arterial Oxygen Saturation, Vol. %	Hematocrit Reading	Cause of Death
8	Left common carotid.....	9.3	16.8	93	Shock
8	(No anastomosis).....	12.0	22.8	92	Cardiac insufficiency
10	Right subclavian (end to end)...	11.5	21.7	100	Pulmonary hemorrhage

oxygen saturation was reported as 95.0 volumes per cent, the usual figure for a normal person. The test has been repeated and verified as the correct determination. In all probability this patient had a pure pulmonary stenosis, without the associated defects.

In table 2 the fatal cases are tabulated showing the systemic vessel used, the red blood cell count, the arterial oxygen saturation, the hematocrit reading and the cause of death. It is seen that in these fatal cases the red blood cell count and the hematocrit readings were unusually high, the hematocrit reading in case 10 being reported as 100. In other words, there was no separation of cells from plasma. Death in the first fatal case is listed as due to shock. The anastomosis had been completed, although the blood pressure or pulse could not be obtained. The child died two hours later, without having regained consciousness. The patient in the second fatal case died before the anastomosis was begun. Death was thought to be due to cardiac insufficiency, as the heart gradually slowed and finally ceased to beat. Postmortem examination showed an atresia of the pulmonary orifice, the entire pulmonary circulation reaching the lungs through a small patent ductus arteriosus. The third fatality was due to pulmonary hemor-

rhage, which occurred four hours after the completion of the operation. This is the only patient in this group who received heparin or dicumarol. Two hours after the operation the temperature was elevated to 102 F., there was some twitching on the opposite side of the body and the patient had not rallied. Believing that cerebral damage was occurring, the initial calculated dose of heparin was given. Two hours later there was a severe pulmonary hemorrhage, and, even though intratracheal suction was quickly carried out, the patient died.

In the patients who survived the procedure there have been few complications.[2] As a rule the patient dies soon after the operation or survives. One patient experienced acute laryngeal edema requiring an

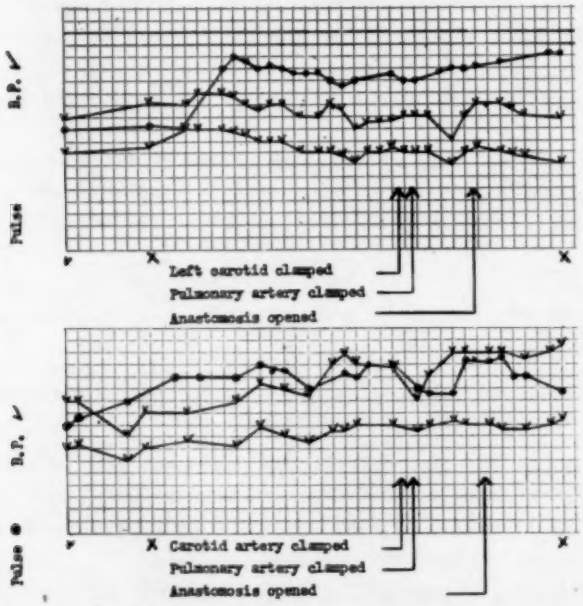

Fig. 1.—The upper chart shows blood pressure during the course of anastomosis of the carotid and pulmonary arteries (technic: carbon dioxide absorption, endotracheal intubation). No significant fall in blood pressure occurred. Cyclopropane and oxygen were used, and the result was good. The lower chart shows no significant fall in blood pressure in anastomosis of the carotid and pulmonary arteries (technic: carbon dioxide absorption, endotracheal intubation). Cyclopro pane and oxygen were used, and the result was good.

emergency tracheotomy. Another patient had a pneumothorax after the operation, and the lung could not be reexpanded for a period of three weeks, even though constant suction to the lung by means of a needle in the chest was maintained. It was thought that the visceral pleura had been torn or severely damaged. The occurrence of serosanguinous fluid in the pleural space has been so common that it is not

2. Harmel, M. H., and Lamont, A.: Anesthesiology **7**:477 (Sept.) 1946.

regarded as a complication. Aspiration is resorted to at the least sign of fluid in physical examination. Usually a sufficient amount of fluid is obtained to warrant the procedure. In 1 patient definite cerebral thrombosis developed, but the patient survived and has now almost completely recovered. The subclavian artery was used for the transplant, and the common carotid was not disturbed. Apparently periods of hypotension during the procedure adds greatly to the operative risk. In figure 1, which is the anesthesia charts, there is seen in the upper chart a slight drop in blood pressure when the carotid was clamped and a slight rise when the pulmonary artery was clamped. However, there is no great change in either direction. The lower chart also shows that no significant change has taken place. One can predict that such a patient will, as a rule, do well in the postoperative period. On

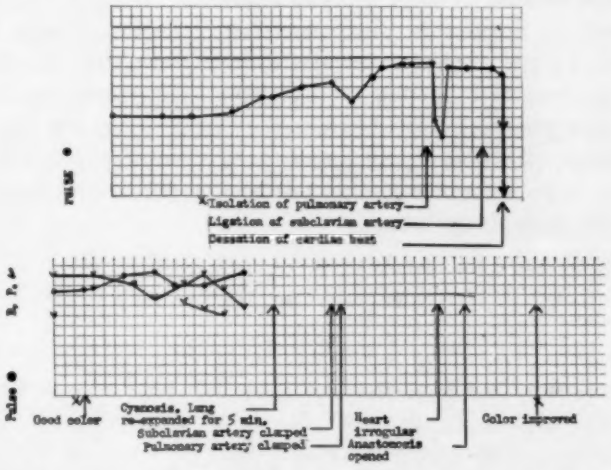

Fig. 2.—The upper chart shows that the blood pressure was not obtainable at any time in an attempted anastomosis of the subclavian and pulmonary arteries (technic: carbon dioxide absorption, endotracheal intubation). Cyclopropane and oxygen were used. The patient died on the operating table. The lower chart shows that the blood pressure was not obtainable before the vessels were clamped and the pulse was not obtainable. Anastomosis was completed, and the blood pressure later returned to normal, but the patient died six hours after operation. Anastomosis was of the subclavian and pulmonary arteries, and cyclopropane and oxygen were used (technic: carbon dioxide absorption, endotracheal intubation).

the other hand, figure 2 shows the anesthesia charts in a fatal case. Blood pressure was not obtainable at any time. During the isolation of the pulmonary artery there was a decided fall in the pulse rate. Death occurred before the operation was completed. The lower chart shows serious fall in blood pressure before the anastomosis was begun. The operation was completed, and the blood pressure and pulse returned, but the patient did not survive. It is highly desirable, therefore, that sufficient circulation to the brain be maintained in these cyanotic

patients. Periods of rest for the patient, when the lung is reexpanded, helps a great deal to maintain an even blood pressure and pulse. It might even be wise to discontinue the procedure until another day if the circulation cannot be adequately maintained before the anastomosis is begun.

One patient in this group deserves special mention because of his mental state. A 4½ year old boy showed decided evidence of mental deficiency. He could not talk and could not be taught the simple acts of obedience in the home. He acted as though he had no cerebrum. After the operation and while he was convalescing the nurses began to notice that the child took interest in things about him. He pointed to the food he desired, and he began to play with toys. He is now in a kindergarten school, and his teacher informs me that, in her opinion, this child will be able to enter a regular school.

ADDENDUM.—Since this paper was read, there has been sufficient time to observe the mental state of this patient. Although there was decided improvement following the operation, the mental status is now apparently not progressively improving.

Since the preparation of this paper, 11 additional patients have been operated on, with 1 fatality. This death was due, at least in part, to acute laryngotracheobronchitis.

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ANESTHETIC MORTALITY IN INTRATHORACIC SURGERY

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AND

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DURING the past thirteen years rapid advancement has been made in the surgical management of intrathoracic lesions. In 1933 Graham [1] performed the first successful removal of the entire lung for carcinoma of the bronchus. Adams and Phemister [2] made the first successful one stage resection of the lower part of the esophagus and esophagogastrostomy for carcinoma performed through the thorax in 1938. Gross [3] in 1939 reported closure of a patent ductus. Crafoord and Nylin [4] in 1944 were the first to relieve successfully the ill effects of coarctation of the aorta by resection and anastomosis. Blalock and Taussig [5] in 1944 performed the first operation in human beings for the correction of pulmonary stenosis.

Intrathoracic surgery is accompanied with many unusual surgical and anesthetic hazards. The dangers of an open pneumothorax were understood by Andreas Vesalius,[6] who in 1555 demonstrated to his students at Padua not only the untoward effects on the cardiorespiratory mechanism of open pneumothorax, with its alterations of intrathoracic pressures, but also a means of avoiding or overcoming them. For cen-

From the Department of Surgery of the University of Chicago.

1. Graham, E. A., and Singer, J. J.: Successful Removal of Entire Lung for Carcinoma of Bronchus, J. A. M. A. **101**:1371-1374 (Oct. 28) 1933.

2. Adams, W. E., and Phemister, D. B.: Carcinoma of the Lower Thoracic Esophagus: Report of a Successful Resection and Esophagogastrostomy, J. Thoracic Surg. **7**:621 (Aug.) 1938.

3. Gross, R. E., and Hubbard J. P.: Surgical Ligation of a Patent Ductus Arteriosus, J. A. M. A. **112**:729-731 (Feb. 25) 1939.

4. Crafoord, C., and Nylin, G.: Congenital Coarctation of the Aorta and Its Surgical Treatment, J. Thoracic Surg. **14**:347-361 (Aug.) 1945.

5. Blalock, A., and Taussig, H. B.: The Surgical Treatment of Malformations of the Heart, J. A. M. A. **128**:189-202 (May 19) 1945.

6. Vesalius, A.: De corporis humane fabrica, libre septum; cited by Bradshaw, H. H.: Anesthesia for Intrathoracic Operations, J. Thoracic Surg. **8**: 293-299 (Feb.) 1939.

turies the dangers of an open pneumothorax were remembered, but the means of obviating these dangers were not applied to problems in intrathoracic surgery.

The need for intrathoracic operations arises frequently in the management of neoplastic, inflammatory and congenital lesions of the organs

TABLE 1.—*Intrathoracic Operations Performed on Six Hundred and Eighty-Eight Patients*

Operation	Number
Pneumonectomy	48
Bilobectomy or partial pneumonectomy	37
Lobectomy	79
Miscellaneous exploratory thoracotomies (mostly for carcinoma)	44
Heart or great vessels	33
Mediastinum	37
Esophagus and cardia	149
Repair of diaphragm through the chest	14
Massive resection of the chest wall	15
Sympathectomy	109
Vagotomy	85
Extrapleural pneumonolysis and plombage	38
Total	688

TABLE 2.—*Sex Incidence in Six Hundred and Eighty-Eight Intrathoracic Operations*

Operation	Male (Percentage in Parentheses)	Female (Percentage in Parentheses)	Total
Pneumonectomy	41 (85.4)	7 (14.6)	48
Bilobectomy or partial pneumonectomy	20 (54.1)	17 (45.9)	37
Lobectomy	27 (34.6)	51 (65.4)	78
Miscellaneous exploratory thoracotomy (mostly for carcinoma)	35 (78.3)	10 (21.7)	45
Heart and greater vessels	18 (53.1)	15 (46.9)	33
Mediastinum	24 (64.9)	13 (35.1)	37
Esophagus and cardia	125 (83.9)	24 (16.1)	149
Repair of the diaphragm through the chest	8 (57.1)	6 (42.9)	14
Massive resection of the chest wall (some lung also)	9 (60)	6 (40)	15
Sympathectomy	51 (46.7)	58 (53.3)	109
Vagotomy	70 (82.4)	15 (17.6)	85
Extrapleural pneumonolysis and plombage	21 (55.3)	17 (44.7)	38
Totals	449 (68.16)	239 (31.84)	688

within the thorax. Primary carcinoma of the lung comprises approximately 8 per cent of all malignant tumors. In men over 20 years of age carcinoma of the esophagus is fourth in frequency of all malignant tumors. It is said to be surpassed in frequency only by carcinoma of the stomach, lung and rectum.[7] Also, carcinoma of the cardiac end

7. Adams, W. E.: Some Recent Accomplishments of Thoracic Surgery, Arch. Surg. **50**:277-285 (June) 1945.

of the stomach is resected either transthoracically or, much less frequently, by thoracolaparotomy.

Many of these patients are grave anesthetic and surgical risks. Because of the nature of the lesions, a large percentage of the patients

TABLE 3.—*Age Incidence*

Operation	Years								
	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	80 to 89
Pneumonectomy	..	1	2	2	16	17	10	..	..
Bilobectomy or partial pneumonectomy	2	6	12	8	4	2	2	1	..
Lobectomy	6	13	32	10	7	7	4	..	..
Miscellaneous exploratory thoracotomy (mostly for carcinoma)	..	1	1	2	11	23	5	..	..
Heart and greater vessels	6	10	6	5	5	..	1	..	..
Mediastinum	1	2	3	9	8	11	2	1	..
Esophagus and cardia	1	2	3	5	24	45	55	10	5
Repair of the diaphragm through the chest	1	..	1	1	5	4	..	1	..
Massive resection of the chest wall (some lung also)	2	2	1	1	3	4	1	1	..
Sympathectomy	..	8	14	36	39	12	..	..	..
Vagotomy	..	4	4	20	22	30	6	..	..
Extrapleural pneumonolysis and plombage	..	2	6	14	12	3	1	..	..
Totals	19	51	85	113	156	158	87	14	5

TABLE 4.—*Physical State*

Operation	Good	Fair	Poor	Serious	Emergency Serious
Pneumonectomy	2	15	20	11	..
Bilobectomy or partial pneumonectomy	..	15	16	5	1
Lobectomy	5	30	39	5	..
Miscellaneous exploratory thoracotomy (mostly for carcinoma)	4	12	16	9	2
Heart and great vessels	..	4	16	13	..
Mediastinum	8	12	12	4	1
Esophagus and cardia	10	61	64	14	1
Repair of the diaphragm through the chest	3	6	3	..	1
Massive resection of the chest wall (some lung also)	2	9	3	1	..
Sympathectomy	..	20	69	20	..
Vagotomy	53	30	3	..	..
Extrapleural pneumonolysis and plombage	..	16	10	10	2
Totals	87	230	271	92	8
Percentage	12.7	33.4	39.3	13.3	1.2

are dehydrated and undernourished, anemic, coughing and dyspneic and have other manifestations of serious alterations in their cardiorespiratory mechanisms. Because of the serious anesthetic and surgical risk, it seemed timely to investigate the outcome in intrathoracic operations

and to determine the relationship of the deaths to the anesthetic management.

The series of 688 intrathoracic operations presented here represents the work of nine surgeons and twenty physician-anesthetists. The greater share of the operations were made by two general surgeons who specialize in thoracic work and three resident surgeons whom they have trained. Some of the sympathectomies were performed by two neurosurgeons. The vagotomies were made by two general surgeons as well as by one of the aforementioned thoracic surgeons. Five faculty physicians and fifteen residents made up the group of twenty physician-anesthetists.

The operations performed are listed in table 1.

Table 2 presents the sex variation in the series of patients. Four hundred and forty-nine, or 68.16 per cent, were males, and 239, or 31.84 per cent, were females. It is noteworthy that the females exceeded the males only in the group who had lobectomy (mostly for bronchiectasis) and in the group who had sympathectomy for malignant hypertension. Eighty-five and four-tenths per cent of those who underwent pneumonectomy were males, as were 83.9 per cent of those who had operations on the esophagus and cardia and 82.4 per cent of those who had vagotomy for peptic ulcer.

The age incidence of these patients appears in table 3. It is of interest that the operations performed on patients below 10 years of age were mainly lobectomies for bronchiectasis and intervention for cardiac lesions. Also there were few operations on the esophagus or cardia in patients under 40 years of age, while 115, or 77.18 per cent, of the patients who had this type of operation were over 50. The majority of patients were above 60 years of age, and 5 were over 80.

The physical state of the patients is revealed in table 4. Only 87, or 12.7 per cent, were in good physical condition, while 230, or 33.4 per cent, were in fair physical condition. Three hundred and seventy-one, or 53.8 per cent, were in poor or serious preoperative condition.

The best risks were in the group having vagotomies for peptic ulcer. From 85 operations in this category there was only 1 death, which occurred early in the series. Regurgitation and aspiration from acute dilatation of the stomach developed after a patient was ambulatory on the second postoperative day, and death ensued on the seventh postoperative day from aspiration pneumonia. This hazard is now eliminated by the judicious aspiration of the stomach postoperatively.

Table 5 presents the incidence, time and cause of death in the total series of 688 operations. Fifty-nine, or 8.5 per cent, of the patients died. The 6 deaths (0.9 per cent) in the operating room were unrelated to anesthesia. They were due to uncontrolled hemorrhage in 3 patients,

tumor thrombus in the heart in 2 and coronary occlusion from the intracardiac operation in 1.

The greatest number of deaths (15) occurred one to three days postoperatively. It is difficult to differentiate the role of anesthesia, operation and physical status in the deaths from circulatory failure, pulmonary involvement and uremia during this period. The death from tracheal perforation was from a surgical accident. There had been no intrinsic trauma or irritation of the trachea during anesthesia.

Table 6 classifies the deaths as to their apparent cause. There were no deaths due to the anesthesia alone. Of the deaths, 11.86 per cent, or 1.01 per cent in the total series, were due to a combination of anesthesia and operation, while 15.26 per cent (or 1.3 per cent in the total series of operations) were due to the operation per se. Twenty-three and seven-tenths per cent (2.03 per cent of the series) were due to the operation and the disease, and the same percentage were due to the disease alone. Of the 14 deaths grouped under "sepsis or late surgical accidents," 5 were due to sepsis, 1 to morphine overdosage, 1 to uremia from sulfathiazole, 2 to uremia from nonanesthetic causes, 4 to separation of sutures and 1 to suicide, making up 23.73 per cent of the total deaths or 2.03 per cent in the series of 688 operations.

COMMENT

Gillespie [8] found a total of 283 deaths during anesthesia for all types of surgical procedures in 227,546 patients in five teaching hospitals on three continents, making a mortality rate of 0.12 per cent. Waters and Gillespie [9] reported 47 deaths in the operating room during anesthesia for 44,894 operations of all types, an immediate mortality of 0.104 per cent. Of the 47 deaths, 8, or 17.9 per cent, occurred during intrathoracic operations. Death was due to hemorrhage in 4 patients, hypoxia in 2, obstruction in 1 and circulatory failure in 1. They emphasized the fact that the particular anesthetic agent used is of less importance than its judicious application.

Trent and Gaster [10] reported 38 sudden deaths during anesthesia for 54,128 operations of all types, or 0.702 per thousand. They had 27 so-called anesthetic deaths during general and spinal anesthesias for 39,880 operations of all types, or 0.677 per thousand.

How can deaths during or following intrathoracic surgery be minimized or avoided?

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8. Gillespie, N. A.: Death During Anaesthesia, Brit. J. Anaesth. **19**:1-16 (Jan.) 1944.

9. Waters, R. N., and Gillespie, N. A.: Deaths in the Operating Room, Anesthesiology **5**:113-128 (March) 1944.

10. Trent, J. C., and Gaster, E.: Anesthetic Deaths in 54,128 Consecutive Cases, Ann. Surg. **119**:954-958 (June) 1944.

TABLE 5.—*Cause and Time of Death*

Operation	Number of Cases	Deaths		In Operating Room	After Operation						
		Number	Per Cent		1 to 3 Days	4 to 7 Days	7 to 14 Days	14 to 21 Days	One Month	Two Months	Three Months
Pneumonectomy	48	15	31.2	2 from hemorrhage	1 from pulmonary edema; 2 from pulmonary emboli	1 from circulatory failure	3 from circulatory failure; 1 from carcinoma of the lung; 1 from bronchial pneumonia; 1 from a cerebral accident	1 from uremia (from sulfathiazole)	1 from sepsis; 1 from separation of sutures	.....	.....
Bilobectomy and partial pneumonectomy	87	1	2.7	.....	1 from circulatory failure						
Lobectomy	79	6	7.5	1 from tumor thrombus in heart	.....	.....	1 from lobar pneumonia; 2 from circulatory failure	.....	1 from pulmonary embolism	.....	1 from bronchial pneumonia
Miscellaneous exploratory thoracotomy	44	3	6.8	1 from tumor thrombus in heart	1 from cardiac failure	1 from carcinoma of the lung					
Heart and great vessels	33	2	6.0	1 from coronary occlusion from operation	.....	.....	.....	.....	1 from the disease (fibrosis of pleura and peritonitis)		
Mediastinum	37	1	2.7	1 from hemorrhage	.....						

Esophagus and cardia.....	149	23	15.4	.....	1 from trachea perforation; 1 from pulmonary edema; 1 from circulatory failure; 1 from other respiratory causes; 1 from bronchial pneumonia; 1 from sepsis; 2 from uremia	2 from circulatory failure; 1 from carcinoma; 2 from separation of sutures; 2 from sepsis; 1 from pulmonary embolism; 1 from postoperative aspiration pneumonia	1 from carcinoma with pleural effusion; 2 from coronary occlusion; 1 from wound infection	1 from lobar pneumonia with empyema	1 from wound separation with empyema		
Massive resection of the chest wall	15	2	13.3	.....	1 from circulatory failure	1 from morphine overdosage					
Sympathectomy.....	109	3	2.7	.....	1 from cerebral accident	.....	.....	.....	1 from circulatory failure	1 from uremia	
Vagotomy.....	85	1	1.1	.....	.....	.....	1 from aspiration pneumonia (regurgitation after being ambulatory)				
Extrapleural pneumonolysis or plombage	38	2	5.2	.....	.....	.....	.....	.....	1 from pulmonary hemorrhage and tuberculosis	.....	1 from suicide

Preoperative Preparation.—The dehydrated and undernourished patients should receive adequate fluids parenterally administered and plasma and blood transfusions in order to get the fluid and electrolyte balance as well as the plasma protein level as near normal as possible. If esophageal obstruction is not too severe, they should receive a high caloric liquid diet to improve their general condition.

Vital capacity, as well as plasma protein levels and hematocrit readings, must be determined before the operation.

Fluid or secretions must be removed from the esophagus, stomach or respiratory tract before anesthesia. With gastric or esophageal lesions this is easily managed by the use of an aspiration catheter. Pulmonary secretions should be removed as well as possible preoperatively by bronchoscopy and the frequent use of dependent drainage, particularly just before the patient comes to the operating room.

TABLE 6.—*Anesthesia, Operation and Disease as Causes of Death in Intrathoracic Operative Procedures*

Cause of Death	Number	Percentage of 59 Deaths	Percentage of 688 Operations
Anesthesia	0	0	0
Operation	9	15.26	1.31
Operation and disease	15	25.42	2.18
Anesthesia and operation	7	11.86	1.02
Sepsis or late surgical accidents	14	23.73	2.03
Disease	14	23.73	2.03
Total deaths	59		8.57

Premedication should be adequate enough to dispel apprehension, facilitate induction and yet not to make sputum more tenacious. Oversedation, with respiratory depression, must be avoided. Most of our patients received premedication one to one and one-half hours before the start of anesthesia. Morphine in dosages of 0.0075 to 0.015 Gm. combined with calcium pentobarbital, 0.09 to 0.27 Gm. by rectum in 30 to 50 cc. of water, or pentobarbital sodium, 0.12 to 0.24 Gm. intramuscularly, were the drugs most frequently employed.

Anesthetic Management.—Early in the twentieth century Von Mikulicz,[11] Sauerbruch,[12] Meltzer and Auer,[13] and Elsberg[14] worked

11. Von Mikulicz, cited by Killian, H.: Scope and Utility of Differential Pressure in Thoracic Surgery, Anesth. & Analg. **17**:154-162 (May-June) 1938.

12. Sauerbruch, E. F.: Present Status of Surgery of the Thorax, J. A. M. A. **51**:808-815 (Sept. 5) 1908.

13. Meltzer, S. J., and Auer, J.: Continuous Respiration Without Respiratory Movements, J. Exper. Med. **11**:622, 1909.

14. Elsberg, C. A.: The Value of Continuous Intratracheal Insufflation of Air in Thoracic Surgery, M. Rec. **77**:493, 1910.

on mechanical methods of solving anesthetic management in intrathoracic surgery. At the present time four methods of anesthetic management are employed in this type of surgery: (1) anesthesia by the endotracheal technic,[15] (2) anesthesia by the face mask technic with positive pressure,[16] (3) high spinal anesthesia [17] and (4) local anesthesia.[18]

The maintenance of the anesthetic state is but a small part of the problem in intrathoracic procedures. Adequate pulmonary ventilation at all times is of most importance and is the responsibility of the anesthetist. Undue alteration in the cardiorespiratory mechanism must be prevented.

The two most important problems for the anesthetist are the prevention of anoxia and the removal of foreign material from the trachea and bronchi.

Good postural drainage should be provided throughout anesthesia. Often in severe cases of increased pulmonary secretion the air passages may become obstructed if good postural drainage and adequate oral suction are not employed during induction of general anesthesia and before the plane of narcosis has been reached. This difficulty arises before the plane of narcosis has reached a sufficient depth to permit the introduction of an endotracheal catheter, if that method is employed. The difficulties that may be encountered by the anesthetist with endotracheal anesthesia in intrathoracic surgery have been thoroughly discussed by Maier.[19]

A longer induction period is required if the endotracheal technic is to be employed, which prolongs the total period of anesthesia. Intubation, if employed, must be carefully and expertly performed under deep anesthesia, without local injury and without producing even momentary anoxia, as patients undergoing thoracic operations are less able to tolerate hypoxia or additional manipulative procedures than the average surgical patient. We have not considered it imperative to introduce an endotracheal catheter if a clear airway is evident during induction, and

15. Dunlap, J. G.: Anesthetic Practices in Thoracic Surgery, Anesth. & Analg. **18**:301-311 (Nov.-Dec.) 1939.

16. Phillips, F.; Livingstone, H. M., and Adams, W. E.: A Clinical Consideration of Anesthesia in Intrathoracic Operations, Anesth. & Analg. **20**:78-87 (March-April) 1941.

17. Magill, I. W.: Anaesthesia in Thoracic Surgery, with Special Reference to Lobectomy, Proc. Roy. Soc. Med. (Sect. Anaesth.) **29**:7-16 (April) 1936.

18. Overholt, R. H.; Wilson, N. J., and Langer, L.: Further Experience in Pulmonary Resection in the Treatment of Pulmonary Tuberculosis, read at the meeting of the American Association for Thoracic Surgery, Detroit, May 31, 1946.

19. Maier, H. C.: Responsibility of the Anesthetist in Reducing the Operative Complications of Thoracic Surgery, Anesthesiology **5**:11-21 (Jan.) 1944.

we have experienced no difficulty in producing adequate positive pressure by the use of an oral airway, a tight-fitting face mask and an anesthesia machine which gives positive pressure. Suction of the oral and pharyngeal areas, aided by a position of the patient favoring drainage during the operation, has seemed satisfactory. The majority of the patients have immediate postoperative bronchoscopic aspiration while still in the operating room. Oxygen is administered during bronchoscopy.

The lateral recumbent position for intrathoracic procedures causes more respiratory difficulty than the supine position; hence it is a wise practice to induce anesthesia with the patient in the latter position and, after good surgical anesthesia and a patent airway has been established, then to place and secure the patient in a proper position which interferes least with the pulmonary ventilation.

Cooperation between the anesthetist and the surgeon is essential. The surgeon must always be kept informed of the actual condition of the patient, for he may be able to assist in overcoming any difficulties or to modify his surgical management to prevent a disaster.

Increased respiratory effort on the part of the patient indicates inadequate pulmonary ventilation. This may be due to obstruction in the air passages or to inadequate inhalation pressure of oxygen. The detrimental effects of anoxia may lead to cardiac failure as well as to damage to the central nervous system. It is questionable if controlled respiration is a safe procedure, and most surgeons find it unnecessary.

It has been found that when the inhalation anesthetic agent, combined with an adequate amount of oxygen, is administered with sufficient inhalation pressure, the blood arterial oxygen can be kept at a satisfactory level.[20] Oxygen administered with adequate inhalation pressure is most important. The amount of distention or deflation of the lungs should be controlled by regulating the exhalation pressure rather than by decreasing the inhalation pressure if asphyxia is to be avoided. A normal cardiorespiratory mechanism can be maintained through proper control of inhalation pressure and the judicious use of analeptics or other drugs when indicated. It is also assisted by the prompt replacement of any fluid or blood loss.

Intrathoracic operations should not be started without a cannula being in place intravenously and a blood transfusion started or immediately available. White and Buxton[21] found an average loss of blood of 1,607.5 cc. in 10 lobectomies and an average loss of 1,458 cc. in 6 pneu-

20. Thornton, T. F., Jr.; Martin, R. C.; Livingstone, H M., and Adams, W. E.: The Effect of Variations of Intratracheal Pressure and Anesthetic Mixtures on the Arterial Blood Oxygen, Anesthesiology **6**:498-504 (Sept.) 1945.

21. White, M. L., Jr., and Buxton, R. W.: Blood Loss in Thoracic Operations, J. Thoracic Surg. **12**:198-202 (Dec.) 1942.

monectomies. The investigation of Thornton, Adams and Schafer [22] substantiated these findings. It is necessary to replace promptly all blood lost during the surgical procedure if shock is to be avoided. In addition, it has been found that after pneumonectomy the pleural fluid which accumulates in the remaining space contains 4 to 5 Gm. of protein per hundred cubic centimeters. Since this space usually has a capacity of between 700 and 1,000 cc., the amount of protein thus removed from the circulating blood and the body tissues is considerable. Hypoproteinemia, with its resulting ill effects, can be avoided by filling this pleural space with plasma at the time of the operation, as advocated by Adams and his associates,[23] in addition to administering an adequate amount of blood or serum intravenously.

Anesthetic drugs having the least tissue toxicity and a minimum of depression to the respiratory mechanism should be employed, and an effort should be made to have the patient awake as soon as possible after the procedure. We most frequently employ ethylene-oxygen induction and add ether with an increased amount of oxygen during maintenance. The snug-fitting face mask with a positive inhalation pressure of 4 to 8 mm. of mercury was employed throughout except in a few vagotomies, in which for teaching purposes cyclopropane, oxygen and ether were used endotracheally.

Just before the chest is closed the anesthetist should gently reinflate the lung with moderately increased positive pressure, so as to reexpand, under direct vision, any atelectatic areas. Overdistention and tension on suture lines must be avoided. At the close of the operation the residual air in the pleural cavity is aspirated by the use of a pneumothorax apparatus until the pressures are within normal limits (8 to 16 cm. of water).

Routine bronchoscopic aspiration of mucopus and blood from the tracheobronchial tree is indicated in the operating room before the patient recovers consciousness.

Postoperative Management.—Oxygen therapy should be instituted as soon as the patient returns from the operating room. Nasopharnygeal insufflation of 10 to 12 liters per minute of humidified oxygen is a simple and efficient method of management. A patent airway must be maintained. Bedside suction is extremely necessary, and mucus and other secretions in the upper air passages must be removed promptly. The endotracheal aspiration technic of Haight [24] is a valuable procedure in

22. Thornton, T. F., Jr.; Adams, W. E., and Schafer P. W.: Hypoproteinemia in Thoracic Surgery, Surg., Gynec. & Obst. **79**:368-373 (Oct.) 1944.

23. Adams, W. E.; Thornton, T. F., Jr., and Carlton, L. M. Jr.: The Use of Blood Plasma for Filling the Pleural Space Following Total Pneumonectomy, Ann. Surg. **122**:905-916 (Dec.) 1945.

24. Haight, C.: Intratracheal Suction in the Management of Postoperative Pulmonary Complications, Surgery **6**:445-449 (Sept.) 1939.

some patients. When this method does not suffice for the removal of tenacious bronchial secretions, bronchoscopy should be employed.

During the first twenty-four hours after surgical intervention, an apparatus for the administration of oxygen with positive pressure should be kept readily available. It is rarely needed but is a valuable safeguard in case of emergency.

The surgeon should use continuous suction drainage applied to a stab wound drain of the pleural cavity except after pneumonectomy. This prevents an accumulation of exudate and maintains the lungs in complete expansion. Usually a double Wangensteen apparatus is employed, which maintains a siphonage of 25 to 30 cc. of water.

Adequate water and mineral balance must be maintained through the use of intravenously and subcutaneously administered fluids as long as necessary. After resection of the esophagus, nothing by mouth is advisable for at least four to five days. Transfusions of blood and plasma should be repeated whenever indicated to prevent postoperative shock, anemia and hypoproteinemia and to hasten convalescence. The hematocrit reading has been a much better index than the red blood cell count or the hemoglobin value for the determination of the true state of the oxygen-transporting medium.[25]

SUMMARY

A series of 688 intrathoracic operations are presented, and the death of 59, or 8.57 per cent, of the patients is discussed. An attempt has been made to determine the relationship of the deaths to the anesthetic and surgical management. The principles that should be observed in the management of patients undergoing intrathoracic procedures are presented in an effort to reduce the incidence of fatalities from this type of surgical treatment.

In comparison with the reported death rates in the operating room for all types of operations, the incidence of deaths from operations of the magnitude of intrathoracic procedures is not high in view of the patients' preoperative physical status.

25. Adams, W. E.; Thornton, T. F.; Carlson, A. J., and Livingston, H. M.: Anoxia and Anesthesia in Intrathoracic Operations, Surgery **13**:859-879 (June) 1943.

ASCORBIC ACID, THIAMINE, RIBOFLAVIN AND NICOTINIC ACID IN RELATION TO ACUTE BURNS IN MAN

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ALTERATIONS in the metabolism of proteins, carbohydrates and electrolytes following burns have been extensively studied in the past few years. In contrast, few investigations of possible changes in vitamin metabolism following burns have been made. Uzbekov,[1] Clark and Rossiter [2] and Harkins [3] have reported decreased ascorbic acid content of the adrenal cortex in burned guinea pigs and rabbits, while Lam [4] has reported a decrease in the plasma ascorbic acid concentration in

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) and the Burns Assignment of the Surgical Services, Boston City Hospital, the Department of Medicine and Surgery, Harvard Medical School, and the Fatigue Laboratory of the Harvard Business School.

1. Uzbekov, G. A.: Problem of Avitaminoses: Effect of Burns on Metabolism of Vitamin C, Klin. med. **15**:237-240, 1937.

2. Clark, E. J., and Rossiter, R. J.: Carbohydrate Metabolism After Burning, Quart. J. Exper. Physiol. **32**:279-300, 1944.

3. Harkins, H. N.: Present Status of the Problem of Thermal Burns, Physiol. Rev. **25**:531-572, 1945.

4. Lam, C. R.: Chemical Pathology of Burns: Collective Review, Surg., Gynec. & Obst. **72**:390-400, 1941.

patients with extreme burns. Andreae, Schenker and Browne [5] found that patients with burns or fractures characteristically showed a pronounced retention of riboflavin during the first three to five days after injury. This was followed by a period of similar duration in which there occurred an increased loss of riboflavin in the urine. About ten days after injury the riboflavin balance returned to normal. They suggested that the riboflavin retained during the first period was stored in some way and subsequently released. Later, during the convalescent period, both nitrogen and riboflavin were retained, 0.3 mg. of riboflavin being retained for each gram of nitrogen. Andreae and Browne,[6] in a later report, confirmed these observations, and in addition reported a high retention of ascorbic acid in similar patients in the early days after injury, which, in contradistinction to the retention of riboflavin, was not followed by a period of increased loss of ascorbic acid. This, they expressed the belief, could not be attributed to preexisting deficiency, faulty absorption, impaired excretion, retention in the tissues or in the edema fluid or excretion in the form of dehydroascorbic acid.

The present study is concerned with the alteration in the plasma concentration of ascorbic acid and in the urinary excretion of ascorbic acid, thiamine, riboflavin and N-methylnicotinamide in patients with burns admitted to the Boston City Hospital during 1944-1945.

METHODS

The patients studied were cared for by members of the Burns Assignment of the Surgical Services of the Boston City Hospital. The dietary calculations were made by a research dietitian. All hematologic and routine chemical determinations were made by the methods previously published from the Thorndike Memorial Laboratory.[7] Determinations of plasma ascorbic acid were made in the Thorndike Memorial Laboratory by the method of Mindlin and Butler.[8] The determinations of vitamin output were made in the Harvard Fatigue Laboratory, the field methods [9] developed there being used. Both fasting and hourly excretion rates and the excretions after the injection of test doses were determined. Low fasting hourly excretion rates of ascorbic acid, thiamine, riboflavin and N-methylnicotinamide

5. Andreae, W. A.; Schenker, V., and Browne, J. S. L.: Riboflavin Metabolism After Trauma and During Convalescence in Man, Federation Proc. **5**:3, 1946.

6. Andreae, W. A., and Browne, J. S. L., in Proceedings of the Eighth Meeting of the Associate Committee on Army Medical Research, National Research Council of Canada, Ottawa, 1946.

7. Levenson, S. M.; Davidson, C. S.; Lund, C. C., and Taylor, F. H. L.: The Nutrition of Patients with Thermal Burns, Surg., Gynec. & Obst. **80**:449-469, 1945.

8. Mindlin, R. L., and Butler, A. M.: Determination of Ascorbic Acid in Plasma, Macromethod and Micromethod, J. Biol. Chem. **122**:673-686, 1938.

9. Johnson, R. E.; Sargent, F.; Robinson, P. F., and Consolazio, F. C.: Assessment of Nutrition and Metabolic Conditions in the Field, War Med. **7**:227-233 (April) 1945.

together with low excretions of these substances after injection of test doses have been considered indicative of tissue unsaturation.[9] The fasting hourly excretion rates were usually determined three times a week on alternate days. For presentation in some of the accompanying charts and tables and in part of the text, the figures from these determinations and also from the plasma ascorbic acid determinations have been averaged and the weekly average listed. The average fasting hourly excretion of the four vitamins under consideration in normal adult males on a normal diet[9] is represented on the charts by dotted lines at the appropriate levels.

Vitamin supplements were given orally in the form of ascorbic acid tablets and "multicebrin" capsules. These contain the following in each capsule: thiamine hydrochloride, 3.0 mg.; riboflavin, 3.0 mg.; pyridoxine hydrochloride, 1.5 mg.; pantothenic acid, 5.0 mg.; nicotinamide, 25 mg.; ascorbic acid, 75 mg.; distilled natural tocopherols, 10 mg.; vitamin A, 5,000 U.S.P. units, and vitamin D, 1,000 U.S.P. units. Vitamins were given intravenously in the form of single or multiple vitamin preparations.

Saturation tests of vitamins were made in the following manner: After a fasting specimen of blood and a fasting hourly specimen of urine were taken, the test doses were given intravenously. Specimens of blood and of urine were then collected at intervals of one-half, one, two, three and four hours. Two different test doses were used. One, named a "high test" dose, contained 1 Gm. of ascorbic acid, 20 mg. of thiamine hydrochloride, 12 mg. of riboflavin and 200 mg. of nicotinamide. The other, the "low test" dose, contained 250 mg. of ascorbic acid, 5 mg. of thiamine-hydrochloride, 3 mg. of riboflavin and 50 mg. of nicotinamide. The field methods of the Harvard Fatigue Laboratory have been used to study fasting hourly excretions and excretions after "low" saturation tests on many thousands of soldiers in all parts of the world.[9] Both "high" and "low" saturation tests have been made on many normal subjects and scorbutic patients at the Boston City Hospital, and the results of these studies will be published shortly.[10]

The percentage of body surface burned was estimated by the method of Lund and Browder.[11] The depth of burn was classified according to the method of Converse and Robb-Smith.[12] In some cases the depth of burn cannot be estimated accurately on the patient's entry to the hospital and for some time thereafter. For patients who died before an accurate classification of the depth could be made, the area of deep burn was estimated as fairly as possible. Dressings in most instances were dry sterile pressure dressings[13] applied usually without anesthesia. The dressings were changed at one to two week intervals. Grafting was done by the Padgett dermatome technic under cyclopropane anesthesia.

The patients have been divided according to age, children and adults being considered separately. This was done for the following reasons: (1) children are actively growing, (2) the children's wards were better staffed with nurses and (3)

10. Lewis, J.; Davidson, C. S.; Adams, M. A.; Robinson, P.; Paige, R. W.; MacDonald, A. H.; Taylor, F. H. L., and Johnson, R. E.: Unpublished data.

11. Lund, C. C., and Browder, N. C.: Estimation of Areas of Burn, Surg., Gynec. & Obst. **79**:352-358, 1944.

12. Converse, J. M., and Robb-Smith, A. H. T.: The Healing of Surface Cutaneous Wounds: Its Analogy with the Healing of Superficial Burns, Ann. Surg. **120**:873-875, 1944.

13. Levenson, S. M., and Lund, C. C.: Dermatome Skin Grafts for Burns in Patients Prepared with Dry Dressings and With and Without Penicillin, New England J. Med. **233**:607-612, 1945.

the food offered to the children was by and large 'better' than that offered to the adults and usually contained appreciably more vitamins. Each group has in turn been divided into those with 'minor' and those with 'major' burns, the latter group being comprised of patients with more than 15 per cent total burn or more than 9 per cent deep burn.

RESULTS

The cases studied are listed in the tables.

Children.—Minor Burns: Four children (cases 1 to 4) with minor burns were studied. All were in excellent nutritional status on entry to the hospital and none had any complications before or after the burns. The fasting concentrations of plasma vitamin C and the fasting hourly excretion rates of the various vitamins are listed in table 2. In all instances these were within the expected 'normal' range. Saturation tests were performed on 1 patient (case 4) when he was essentially healed, the "high test" dose being injected. The four hour excretions and the plasma vitamin C levels at this time were normal.

TABLE 1.—*Classification of Children with Burns*

Case	Age	Sex	Percentage of Body Surface Burned: Total	Deep	Past History	Nutritional Status on Entry	Shock *	Anemia *	Hypoproteinemia *	Local Exudation † (Late)	Food Intake	Nutritional Status on Discharge	Result
1	14	F	3	0	‡	Good	0	0	0	1	Good	Good	Living
2	8	M	3	1	‡	Good	0	0	0	1	Good	Good	Living
3	4	F	6	3	‡	Good	0	0	0	1	Good	Good	Living
4	10	M	10	6	‡	Good	0	0	0	1	Good	Good	Living
5	5	M	30	25	‡	Good	+	+	+	3	Fair	Poor	Dead
6	6	F	65	60	‡	Good	+	0	0	—	Good	Good	Dead

* + signifies present and 0 absent.
† 1 indicates slight, 2 moderate and 3 severe.
‡ Noncontributory.

Severe Burns: Two children (cases 5 and 6) with severe burns were studied. The patient in case 5 was a 5 year old boy, previously healthy, with extensive deep burns. Despite an intake of over 200 Gm. of protein and 4,000 calories daily, it was impossible to keep him in good nutritional status. He gradually lost weight, granulations were absent and local exudation and fever were pronounced. He received large daily supplements of the various vitamins as listed in table 2. The fasting plasma vitamin C level and hourly excretion rates of the vitamins and the response to injection of "high test" doses were determined only in the seventh and the ninth week and were within the expected range.

The patient in case 6 was a 6 year old girl, previously healthy, with an extensive deep burn who was in severe shock for about one hour after her entry to the hospital and again twelve hours later. Fasting hourly excretion rates of ascorbic acid, thiamine, riboflavin and N-methyl-

TABLE 2.—*Fasting Hourly Excretion Rates and Plasma Vitamin C Concentration in Children with Burns*

Weeks

Supplemental

TABLE 2.—*Fasting Hourly Excretion Rates and Plasma Vitamin C Concentration in Children with Burns*

Case	Supplemental Daily Intake	Weeks 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Riboflavin (Output in Micrograms)																									
1	6	..	25	33	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
2	0	..	..	..	..	..	..	..	..	19	18	15	18	25	20	..	..	..	..	..	..	..	..	..	..
3	0	..	29	15	12	13	26	12	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	10	..	..	..	..	..	..	..	50	28	41	41	46	67	40	114	96	77	..	..	..	..	..	..	..
4	0	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	28	37
	10	..	..	..	..	..	20	42	38	35	36	50	43	120	49	44	33	89	49	32	81	110	23	..	..
5	22	..	..	..	..	..	..	320	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	28	..	..	..	..	..	..	..	..	117	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
6	0	5	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Thiamine (Output in Micrograms)																									
1	10	..	12	22	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
2	0	..	..	..	..	..	..	..	..	3	6	12	11	7	9	..	..	..	..	..	..	..	..	..	..
3	0	..	9	4	5	7	32	6	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	10	..	..	..	..	..	..	..	38	30	43	35	30	39	34	35	45	77	..	..	..	..	..	..	..
4	0	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	17	10
	10	..	..	..	..	..	12	17	17	22	43	156	33	58	34	35	21	26	22	15	31	18	10	..	..
5	20	..	..	..	..	..	..	170	..	136	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
6	0	3	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
N-Methyl-nicotinamide (Output in Milligrams)																									
1	70	...	0.5	0.4	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
2	0	...	...	...	...	...	...	...	...	0.1	0.2	0.1	0.1	0.2	0.1	...	...	...	...	...	...	...	...	...	...
	0	...	0.3	0.1	0.1	0.1	0.2	0.0	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
3	70	...	...	...	...	...	...	...	0.3	0.1	0.3	0.3	0.3	0.4	0.3	0.5	0.6	0.4	...	...	...	...	...	...	...
4	0	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	0.4	0.3
	70	...	...	...	...	...	0.1	0.3	0.2	0.2	0.4	0.5	0.3	1.7	0.5	0.3	0.7	0.4	0.4	0.2	0.3	0.4	0.3	...	...
5	250	...	...	...	...	...	...	2.6	...	1.9	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
6	0	0.8	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Ascorbic Acid (Output in Milligrams)																									
1	250	...	2.6	6.9	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
2	0	...	...	...	...	...	...	...	...	1.3	2.5	3.1	1.4	1.0	0.3	...	...	...	...	...	...	...	...	...	...
3	0	...	6.4	1.9	0.4	0.8	5.8	1.4	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	1,000	...	...	...	...	...	...	...	8.0	2.9	...	4.5	2.9	4.3	1.5	3.6	3.3	3.5	...	...	...	...	...	...	...
	0	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	2.0	0.9
4	250	...	...	...	...	...	2.1	3.4	2.4	1.5	4.7	1.4	0.8	9.7	1.6	2.5	0.9	2.3	1.4	1.8	3.6	2.9	1.7	...	...
5	250	...	...	...	...	...	...	51.0	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	500	...	...	...	...	...	...	...	...	1.9	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
6	0	1.5	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Plasma Ascorbic Acid (Milligrams per 100 Cc. Plasma)																									
1	250	...	1.1	0.9	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
2	0	...	...	...	...	...	...	...	...	1.1	1.1	1.0	1.1	...	...	...	...	...	...	...	...	...	...	...	...
3	0	...	0.7	0.9	1.3	1.1	1.3	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	1,000	...	...	...	...	...	...	...	1.0	...	0.8	0.6	0.6	...	0.8	...	...	...	...	...	...	...	...	...	...
4	0	...	0.5	...	0.6	...	0.6	0.5	0.6	0.8	0.8	...	...	0.8	...	...	...	...	...	...	...	...	...	...	...
5	250	...	...	...	...	...	...	0.4	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	500	...	...	...	...	...	...	...	0.9	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
6	0	0.7	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...

nicotinamide at the twenty-second hour after injury, before any vitamin supplements were given, were normal. She died on the third day before any further tests were made.

Adults.—Minor Burns: Eleven adults (cases 7 to 17) with minor burns were studied. Little change from normal in the excretion of thiamine, riboflavin, N-methylnicotinamide and ascorbic acid or in the plasma concentration of ascorbic acid was noted except in patients with

TABLE 3.—*Classification of Adults with Burns*

Case	Age, Sex	Percentage of Body Surface Burned		Past History *	Nutritional Status on Entry	Shock †	Anemia †	Hypoproteinemia †	Local Exudation ‡ (Late)	Food Intake	Nutritional Status on Discharge	Result
		Total	Deep									
7	34 M	6	0	0	Good	0	0	0	1	Poor	Fair	Living
8	31 M	8	0	0	Good	0	0	0	1	Poor, then good	Good	Living
9	57 F	3	1	0	Good	0	0	0	1	Good	Good	Living
10	35 M	3	1	0	Good	0	0	0	1	Good	Good	Living
11	52 F	3	1	0	Good	0	0	0	1	Fair	Good	Living
12	28 F	3	1	0	Good	0	0	0	1	Good	Good	Living
13	46 M	3	1	0	Good	0	+	0	1	Good	Good	Living
14	56 F	4	1	0	Fair	0	+	0	2	Fair	Fair	Living
15	24 F	5	2	0	Good	0	+	0	2	Good	Good	Living
16	54 M	5	2	Chronic osteomyelitis	Good	0	0	0	2	Fair	Fair	Living
17	60 M	9	4	Alcoholism, chronic colitis and diarrhea	Poor	0	+	0	2	Good	Good	Living
18	35 F	18	1	0	Good	0	0	0	1	Good	Good	Living
19	42 F	20	2	0	Good	+	0	0	2	Good	Good	Living
20	27 M	40	35	Alcoholism	Fair	0	+	+	3	Good	Fair	Dead
21	33 M	40	35	0	Good	0	0	+	3	Good	Good	Dead

* 0 signifies noncontributory.
† + means present and 0 absent.
‡ 1 indicates slight, 2 moderate and 3 severe.

some complicating factor such as preexisting deficiency, low food intake, high fever, alcoholism or serious infection (table 4). The courses of patients with such complications are given in detail.

CASE 8.—L. A., a 31 year old white man with a noncontributory past history, was admitted to the hospital shortly after receiving dermal burns of his face, scalp, neck and right forearm and hand. The total area of the body surface burned was 9 per cent. His face and neck were treated with frequently changed petroleum gauze strips that were not bandaged. The forearm and hand were treated with a

dry sterile pressure dressing. Because of pain and swelling of the mouth and face, he took no oral feeding during the first week and only small amounts in the second week. He was given feeding intravenously that included 100 Gm. of amigen daily during this time, but he lost 8 pounds (3.6 Kg.) in weight. His temperature ranged as high as 104 F. and as low as 100 F. for one week but became normal thereafter. There was no evidence of any spreading infection at any time. At the time of the first dressing of the arm, at fourteen days, only small scattered areas on the forearm and face were unhealed. When discharged at the end of the fourth week, his burns were healed and he had regained his lost weight. The data on the vitamins are shown in charts 1 and 2.

During the first six days the patient received no vitamin supplements and little oral food. The fasting hourly excretion rates of ascorbic acid, thiamine, riboflavin and nicotinamide were below the average values found in healthy persons on a normal diet. The plasma vitamin C concentration, which was 0.2 mg. per hundred cubic centimeters on the second day, fell to zero on the fourth day. Thereafter it rose to a level of 0.6 mg. on the sixth day. During the second and third weeks he received a supplement of 150 mg. of ascorbic acid daily in the form of orange juice. The hourly excretion rate rose to an average of 4.2 mg. per hour, and the fasting plasma vitamin C level rose to 0.7 mg. per hundred cubic centimeters. A saturation test with 1 Gm. of vitamin C was performed on the ninth day. The four hour excretion was 263 mg., which is below the amount excreted by normal healthy persons on a normal diet. The plasma C level half an hour after the injection of the test dose was also low. We believe that the low excretions of vitamins and the low response to the ascorbic acid saturation test were due to a combination of starvation and burns.

During the third and fourth weeks the supplement of ascorbic acid was increased to 450 mg. daily given orally, and oral supplements of thiamin, riboflavin and nicotinamide were given in amounts of 9, 6 and 60 mg. respectively. The fasting hourly excretion rate of all the vitamins rose from the previous low levels—the ascorbic acid to about 15 mg. per hour, the thiamine to 20 micrograms per hour, the riboflavin to 75 micrograms per hour and the N-methylnicotinamide to 0.5 mg. per hour.

Case 15.—M. G., a 24 year old white woman with a noncontributory past history except for an extremely low intake of all citrus fruits, was admitted to the hospital shortly after receiving flame burns of the arm and chest. The total area of surface burned was 5 per cent and the area of deep burn 2 per cent. Examination revealed a fairly well developed and well nourished woman. There were no physical signs suggestive of disease due to vitamin deficiency. Her temperature remained between 98 and 99 F. for the first ten days but then began to rise, reaching a level of 105 F. on the thirteenth day. A dressing done at this time revealed cellulitis surrounding the burned area. A firm dry pressure dressing and an external plaster cast were applied and the patient started on sulfadiazine. Within three days her temperature came down to 100 F. and in a few days more

TABLE 4.—*Fasting Hourly Excretion Rate of Vitamins in Adults*

Case	Supplemental Daily Intake, Mg.	Weeks 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
							A												
							Riboflavin (Output in Micrograms)												
7	0	38	34	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	6	..	..	86	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
8	0	18	19	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	6	..	..	49	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
9	0	..	..	16	28	29	22	..	..	..	..	..	..	..	..	..	..	..	..
	10	..	..	..	..	..	..	..	125	158	129	229	118	..	..	..	..	..	..
10	0	..	..	..	25	20	29	33	19	14	25	..	..	..	..	..	..	..	..
11	0	..	..	..	..	..	..	..	12	15	..	..	..	..	..	..	..	..	..
12	0	..	..	..	..	..	..	..	..	71	70	69	113	..	63	..	..	..	..
	6	..	..	..	..	..	..	55	69	..	..	..	..	..	..	..	..	..	..
13	6	..	..	80	52	57	95	73	40	93	9	..	..	..	..	..	..	..	..
14	0	..	..	..	..	..	..	..	..	..	..	..	..	44	..	..	..	..	..
	6	..	..	..	..	..	..	..	..	..	125	243	46	..	..	..	..	..	..
15	0	..	..	31	84	36	74	38	..	..	..	35	59	..	..	..	..	..	..
16	0	26	20	22	23	54	..	..	..	..	..	..	..	..	..	..	..	..	..
	10	..	..	..	..	..	53	67	40	62	54	58	68	81	81	99	36	53	..
17	0	12	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	10	..	59	63	75	60	57	..	39	98	149	63	190	275	153	80	195	130	130
18	0	121	95	108	88	8	..	..	..	..	..	..	..	..	..	..	..	..	..
19	0	30	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	10	..	163	86	83	123	28	44	100	30	82	..	..	..	..	..	..	..	..
21	10	..	16	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	20	145	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
							B												
							Thiamine (Output in Micrograms)												
7	0	40	20	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	10	..	..	73	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
8	0	6	7	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	10	..	..	20	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
9	0	..	..	5	6	5	5	..	..	..	..	..	..	..	..	..	..	..	..
	10	..	..	..	..	..	..	..	86	58	38	125	225	..	..	..	..	..	..
10	0	..	..	..	15	10	8	13	14	5	7	..	..	..	..	..	..	..	..
11	0	..	..	..	..	5	3	..	..	..	..	..	..	..	..	..	..	..	..
12	0	..	..	..	..	..	..	..	..	97	35	110	34	..	31	..	..	..	..
	10	..	..	..	..	..	..	73	88	..	..	..	..	..	..	..	..	..	..

B—Continued

Thiamine (Output in Micrograms)

13	10	..	..	30	20	41	..	88	50	50	108	111	..	..	..	..	..	..	..
14	0	..	..	..	..	..	..	..	..	..	..	..	16	..	..	..	..	..	..
	10	..	..	..	..	..	..	..	..	52	84	218	70	..	..	..	..	..	..
	20	..	..	..	..	15	43	66	54	..	..	..	..	..	..	..	..	..	..
15	0	..	..	13	14	6	22	12	..	..	..	8	19	..	..	..	..	..	..
16	0	7	5	6	8	7	..	..	..	..	..	..	..	..	..	..	..	..	..
	10	..	..	..	..	..	42	39	26	25	42	34	38	43	48	45	31	41	29
17	0	6	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	10	..	..	..	..	..	59	47	78	63	81	50	103	66	63	220	41	42	44
	50	..	127	107	128	75	..	..	..	..	..	..	..	..	..	..	..	..	..
18	0	21	22	16	15	2	..	..	..	..	..	..	..	..	..	..	..	..	..
19	0	8	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	10	..	110	44	64	49	25	59	56	38	35	..	..	..	..	..	..	..	..
	20	..	38	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
21	50	138	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..

C

N-Methyl-nicotinamine (Output in Milligrams)

7	0	0.3	0.3	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	70	...	...	0.9	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
8	0	0.4	0.3	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	70	...	...	0.3	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
9	0	...	...	0.2	0.4	0.4	0.2	...	...	...	...	...	...	...	...	...	...	...	...
	70	...	...	...	...	...	...	...	1.0	1.7	0.7	1.1	0.7	...	...	...	...	...	...
10	0	...	...	...	0.2	0.3	0.5	0.5	0.5	0.9	0.3	...	...	...	...	...	...	...	...
11	0	...	...	...	...	...	...	...	0.1	0.2	...	...	...	...	...	...	...	...	...
12	0	...	...	...	...	...	...	...	...	1.4	1.0	1.3	1.1	...	0.8	...	...	...	...
	70	...	...	...	...	...	...	1.3	1.0	...	...	...	...	...	...	...	...	...	...
13	70	...	...	0.7	0.4	0.5	0.9	0.5	0.5	0.8	1.0	...	...	...	...	...	...	...	...
14	0	...	...	...	...	...	...	...	...	...	...	...	...	0.1	...	...	...	...	...
	70	...	...	...	...	...	...	...	...	...	0.6	0.8	0.5	...	...	...	...	...	...
	125	...	...	...	...	0.2	0.4	0.4	0.5	0.9	...	...	...	...	...	...	...	...	...
15	0	...	...	0.3	0.2	0.4	1.0	0.4	...	...	...	0.4	0.7	...	...	...	...	...	...
16	0	0.1	0.1	0.2	0.5	0.5	0.5	...	...	...	...	...	...	...	...	...	...	...	...
	70	...	...	...	...	...	...	0.3	0.4	0.4	0.4	0.3	0.3	0.3	0.6	1.1	0.4	0.4	0.5
17	0	0.3	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	70	...	...	...	...	...	0.7	1.0	1.2	0.6	0.4	0.4	1.2	0.8	0.8	1.6	0.7	0.6	0.9
	750	...	1.1	0.9	2.1	1.3	...	...	...	...	...	...	...	...	...	...	...	...	...
18	0	0.4	0.4	1.2	1.0	0.1	...	...	...	...	...	...	...	...	...	...	...	...	...
19	0	0.3	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	70	...	0.7	0.7	0.6	1.3	0.4	0.8	0.3	0.5	0.6	0.5	...	...	...	...	...	...	...

Patient	Supplemental Daily Intake	Weeks 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
											D													
											Ascorbic Acid (Output in Milligrams)													
7	0	3.2	0.5	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	250	...	...	1.5	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
8	0	1.0	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	250	...	4.2	16.5	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
9	0	...	...	2.5	0.5	0.8	1.5	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	1,000	...	...	...	...	...	...	...	...	9.3	27.6	24.0	39.0	18.0	...	...	...	...	...	...	...	...	...	...
10	0	...	...	...	1.8	1.0	2.5	2.0	1.0	0.2	0.7	...	...	...	...	...	...	...	...	...	...	...	...	...
11	0	...	...	...	...	...	...	...	0.5	0.4	...	...	...	...	...	...	...	...	...	...	...	...	...	...
12	0	...	...	...	...	...	...	...	...	28.0	1.6	2.0	1.9	...	1.8	...	...	...	...	...	...	...	...	...
	1,000	...	...	...	...	...	...	2.4	52.0	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
13	250	...	...	5.0	4.3	4.7	4.5	1.2	1.5	2.5	7.0	...	...	...	...	...	...	...	...	...	...	...	...	...
14	1,000	...	...	...	5.7	5.0	20.0	8.0	12.0	2.3	7.1	19.0	6.0	...	...	...	...	...	...	...	...	...	...	...
15	0	...	...	1.2	1.6	0.7	2.7	2.7	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	1,000	...	...	...	...	...	...	...	...	...	...	16.0	73.0	...	...	...	...	...	...	...	...	...	...	...
16	0	0.3	1.2	0.4	0.5	0.8	1.2	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	1,000	...	...	...	...	...	...	5.3	3.7	5.1	11.2	5.9	9.2	8.7	8.9	10.0	9.0	12.0	...					
17	1,000	...	3.8	12.9	5.8	5.0	10.9	8.8	9.6	12.5	21.0	8.3	12.0	12.0	9.0	19.0	5.0	11.0	6.0					
18	0	1.9	2.5	3.2	4.8	0.4	...	...	...	...	...	...	...	...	...	...	...	...	...					
19	0	0.6	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...					
	250	...	2.2	1.3	3.5	2.6	0.5	0.8	1.6	0.7	0.3	1.5	6.0	...	...	...	...	...	...					
21	500	4.2	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...					
											E													
											Fasting Ascorbic Acid Concentration in Plasma (Milligrams per 100 Cc.)													
7	0	0.5	0.4	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
8	0	0.3	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	250	...	0.8	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
9	0	...	...	0.47	0.3	...	0.7	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	1,000	...	...	...	...	...	...	...	0.9	1.0	0.6	0.6	0.5	...	...	...	...	...	...	...	...	...	...	...
10	0	...	...	...	0.1	0.3	0.2	0.5	0.4	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
11	0	...	...	...	...	...	...	...	...	0.7	...	...	...	...	...	...	...	...	...	...	...	...	...	...
12	0	...	...	...	...	...	...	...	...	1.0	0.9	1.0	0.9	...	...	...	...	...	...	...	...	...	...	...
	1,000	...	...	...	...	1.1	...	1.2	1.1	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
13	250	...	...	0.9	0.9	0.9	1.3	...	0.9	...	1.1	...	...	...	...	...	...	...	...	...	...	...	...	...
14	1,000	...	...	...	0.7	1.0	0.7	...	0.5	0.8	0.5	...	...	0.9	...	...	...	...	...	...	...	...	...	...
15	0	...	...	0.2	0.0	0.0	0.0	0.0	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	1,000	...	...	...	...	...	...	...	...	...	...	...	1.3	...	...	...	...	...	...	...	...	...	...	...
16	0	0.2	0.2	0.3	...	...	0.0	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	1,000	...	...	..	...	...	...	1.0	0.6	...	0.5	...	...	...	...	...	...	...	...	...	...	...	...	...
17	0	0.3	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1.9	0.28	0.7	0.9	0.7
	1,000	...	0.8	...	0.1	...	0.5	0.3	0.6	0.1	0.3	0.1	0.3	0.0	...	0.6	0.3	1.1	1.6	1.0	...	...	...	...
18	0	...	0.4	0.0	0.8	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
19	250	...	0.0	0.7	0.6	0.7	0.9	0.7	1.6	1.0	1.2	...	...	...	...	...	...	...	...	...	...	...	...	...
20	1,000	0.51	0.0	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	2,000	...	...	0.9	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
21	1,000	0.68	0.53	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...

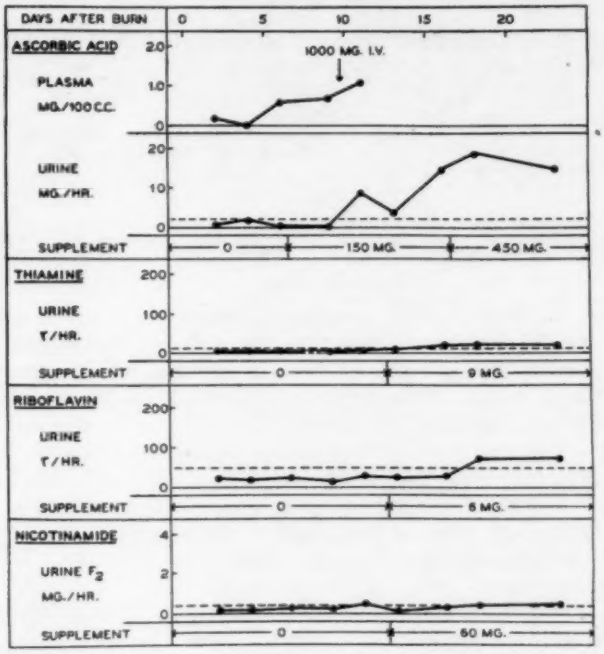

Fig. 1 (case 8).—Plasma ascorbic acid concentration and fasting hourly excretion rates of ascorbic acid, thiamine, riboflavin and N-methylnicotinamide in an adult with a minor burn.

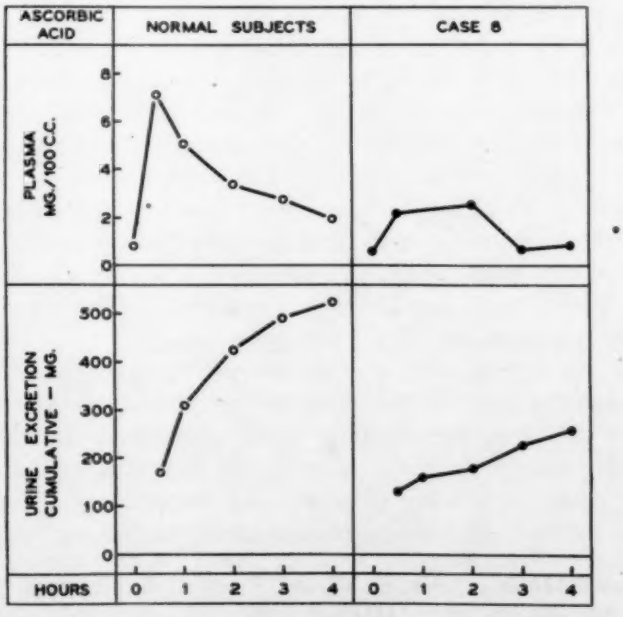

Fig. 2 (case 8).—Ascorbic acid saturation test on the ninth day after injury in an adult with a minor burn. The test dose was 1 Gm.

TABLE 5.—*"Low" Saturation Tests of Vitamin Excretion in Four Hours in a Patient Studied (Case 15)**

Day	Ascorbic Acid, Mg.	Thiamine, Mg.	Riboflavin, Mg.	N-Methyl Nicotinamide, Mg.
47th	13.1	2.4	0.4	13.0
82d	228	1.7	0.4	6.3

* The test doses given (intravenously) were: ascorbic acid, 250 mg.; thiamine, 5 mg.; riboflavin, 3 mg., and nicotinamide, 50 mg.

it was normal, at which level it remained thereafter. The patient's appetite was fairly good, but she continued to take little citrus fruits. The plasma protein concentration varied between 5.5 and 6.3 Gm. per hundred cubic centimeters. There was slight loss of weight. Skin grafting was first done in the seventh week, with only about a 20 per cent take. She was then given 1 Gm. of vitamin C a day, and a second and a third skin grafting were done in the tenth and eleventh weeks, with a 100 per cent take each time. Her weight at this time was 102 pounds (46 Kg.), her weight before entry to the hospital having been 107 pounds (48.5 Kg.). Her further course was benign, and she was discharged in the thirteenth week. The data on the vitamins are given in charts 3 and 4 and in table 5.

No supplements of thiamine, riboflavin or nicotinamide were given throughout the course in the hospital. The fasting hourly excretion rates of these vitamins were normal as were the four hour excretions after the injection of test doses in the seventh and twelfth weeks. In contrast, during the first seven weeks, when no supplement of ascorbic acid was given, although the fasting hourly excretion rates of ascorbic acid were low normal the fasting plasma vitamin C concentrations were extremely low. The four hour excretion after the injection of 250 mg. was exceedingly low on the forty-seventh day, only 13 mg. being excreted. This is approximately the amount excreted after a similar injection in patients with scurvy.[11] The plasma levels of ascorbic acid after the injection of one test dose were also low, being similar to the levels seen in patients with scurvy. We believe that the failure of the first skin graft on this patient was due in part to a deficiency of ascorbic acid of such severity that formation of connective tissue and capillaries was impaired.[14]

From the eighth week the patient was given a supplement of 1 Gm. of ascorbic acid daily. The fasting plasma ascorbic acid level had risen to 1.3 mg. per hundred cubic centimeters four weeks later. The fasting hourly excretion rates in the eleventh and twelfth weeks were extremely high, being 16 and 23 mg. respectively. The four hour excretion in the twelfth week after injection of 250 mg. was 228 mg.,

14. Bartlett, M. K.; Jones, C. M., and Ryan, A. E.: Vitamin C Studies on Surgical Patients, Ann. Surg. **111**:1-26, 1940.

as compared with 13 mg. excreted in the seventh week. The plasma ascorbic acid levels at this time were also normal.

CASE 16.—M. H., a 54 year old white man with a past history of chronic osteomyelitis of the femur, was admitted to the hospital shortly after receiving

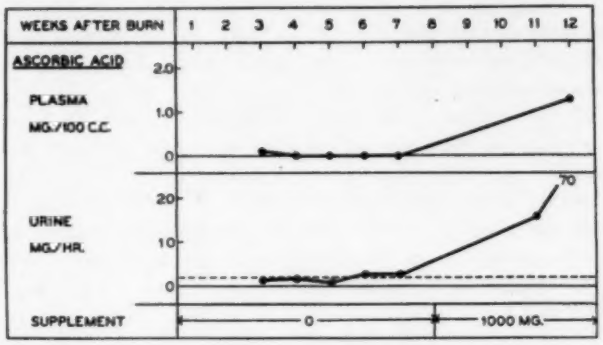

Fig. 3 (case 15).—Plasma ascorbic acid concentration and fasting hourly excretion rates in an adult with a minor deep burn, whose normal intake of ascorbic acid was extremely low.

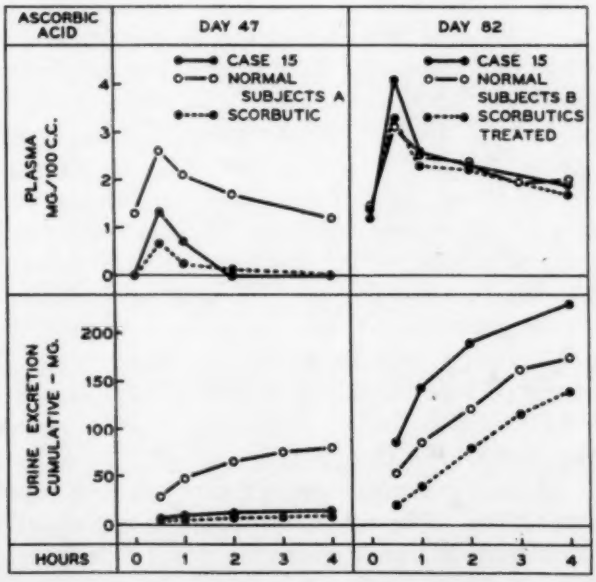

Fig. 4 (case 15).—Ascorbic acid saturation tests in a patient with a minor deep burn, whose normal intake of ascorbic acid was low. The test dose was 250 mg. given intravenously.

flame burns on 5 per cent of his body surface, the burns being deep over a 2 per cent area. Examination revealed a well developed and well nourished man. There were healed deep scars on the left thigh and some varicosities of both legs. He was essentially afebrile throughout his course except for an unexplained rise in temperature to 102.5 F. on the sixth day in the hospital.

During the first two months his appetite was poor, principally because he did not like the food, and his food intake was low. During this time he lost 45 pounds (20 Kg.) in weight. Thereafter, he was placed on a high protein, high caloric diet which was to his liking, principally in the form of amigen or "nutramigen" given in a drink. On this regimen he slowly gained weight. His plasma protein concentration during the first week was 5.6 Gm. per hundred cubic centimeters, with albumin 3.5 Gm. and globulin 2.1 Gm. At the end of two months this had fallen only slightly, the level never going below 5 Gm. for protein and 3 Gm. for albumin. Subsequently the plasma protein remained at this level. His hemoglobin content was 99 per cent during the first week; it fell gradually to 78 per cent at the end of nine weeks and then remained between 80 and 90 per cent thereafter. One transfusion of 500 cc. of blood was given in the ninth week. The osteomyelitis of the femur became active intermittently during his course, as shown by slight purulent discharge which occurred without other evidence of infection in the old wound. Grafting was done for the first time in the eighth week without success. Regrafting two months later was completely successful. The data on vitamins are given in chart 5.

During the first six weeks the patient received no vitamin supplements, but thereafter he received 1 Gm. of ascorbic acid, 10 mg. of riboflavin, 10 mg. of thiamine and 70 mg. of nicotinamide daily.

The fasting plasma ascorbic acid concentration was between 0.2 and 0.3 mg. per hundred cubic centimeters during the first three weeks and then fell to zero during the sixth week. The daily rates of fasting hourly excretion during this time were also low, varying from 0.3 to 1.2 mg. per hour. After the supplement of 1 Gm. of ascorbic acid daily was given, the fasting plasma ascorbic acid concentration rose to from 0.5 to 1.0 mg. per hundred cubic centimeters and the daily rate of fasting hourly excretion to from 3.7 to 11.2 mg. per hour.

During the first four weeks, the fasting hourly excretion rate of riboflavin was low, but it then rose to normal values in the fifth week (about 50 micrograms per hour) before supplements of riboflavin were given. Thereafter, with a daily supplement of 10 mg. of riboflavin the excretion varied between 50 and 80 micrograms per hour.

During the first five weeks, the fasting hourly excretion rate of thiamine was slightly low, but it rose to high normal values in the sixth week (about 40 micrograms per hour) before supplements of thiamine were given. Thereafter, on a daily supplement of 10 mg. of thiamine the fasting hourly excretions varied between 20 and 40 micrograms.

During the first three weeks, the fasting hourly excretion rate of N-methylnicotinamide was 0.1 to 0.2 mg. Subsequently, the rate was about 0.5 mg. per hour and did not change significantly when a supplement of 70 mg. of nicotinamide was given.

As noted previously, grafting in the eighth week was unsuccessful. We believe that although the vitamin deficiencies were corrected prior to the first grafting the protein deficiency had not been corrected and

the graft failed for this reason. Two months later, at which time the patient was in good nutritional status, grafting was completely successful.

CASE 17.—W. W., a 60 year old man, was admitted to the hospital shortly after receiving flame burns of his back and arms when he fell asleep smoking a cigaret in bed while intoxicated. During the year prior to entry, the patient had been on an extremely poor diet and had consumed fairly large quantities of alcohol. He had had bloody diarrhea for the six months preceding entry and during this time had lost 10 pounds (4.5 Kg.) in weight. There had been no ascites, jaundice or edema of the ankles. His past history was otherwise noncontributory.

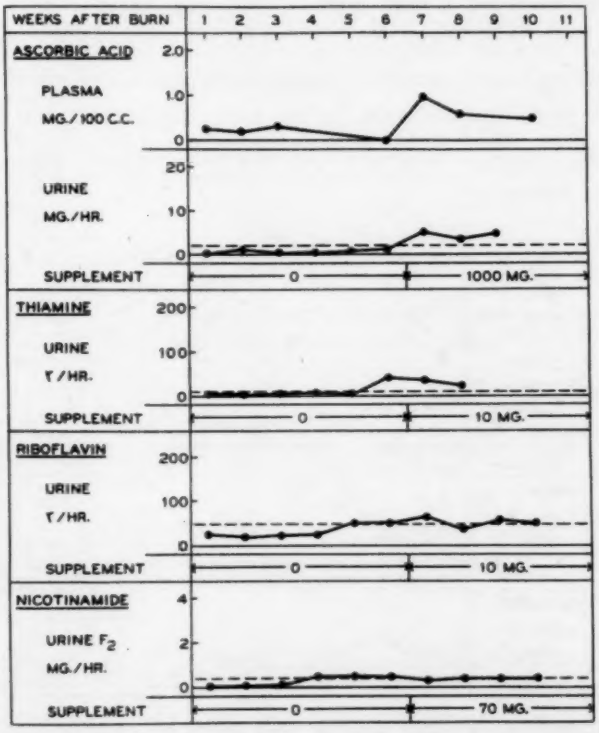

Fig. 5 (case 16).—Plasma ascorbic acid concentration and fasting hourly excretion rates of ascorbic acid, thiamine, riboflavin and N-methylnicotinamide in an adult with a minor deep burn complicated by osteomyelitis.

Examination revealed a poorly nourished elderly man with deep burns of the back and of the upper part of the arms. Otherwise the examination revealed nothing significant. The area of burn was 9 per cent and that of deep burn 4 per cent. There was no initial or subsequent shock. During the first ten days he had intermittent diarrhea, with occasional stools which gave a positive reaction to the guaiac test. His appetite was poor and his food intake low. Sigmoidoscopy at this time revealed nothing abnormal. A series of gastrointestinal roentgenograms and one made after a barium enema, done within the next month and repeated two months later, were also noncontributory.

In the third week the patient was put on a high protein, high caloric diet, given by means of intubation. He had in addition received large doses of vitamins intramuscularly from the second week. The diarrhea and the guaiac-positive stools decreased and finally disappeared. His temperature throughout the first two months ranged between 98.6 and 100 F. and thereafter rarely went above 99 F. One month after his entry to the hospital incision and drainage of a moderate-sized abscess over the right deltoid were done. His weight three weeks after entry was 119 pounds (54 Kg.). This had fallen to 110 pounds (50 Kg.) six weeks later; it gradually rose, reaching 120 (55 Kg.) four months after entry, and by the time of discharge was 128 (58 Kg.). The first skin graft was done in the ninth week, with complete take, and a small graft to cover the remaining areas was done in the twelfth week. The data on the vitamins are presented in chart 6.

The fasting hourly excretion rates of thiamine and riboflavin during the first week after admission, before any supplements had been given,

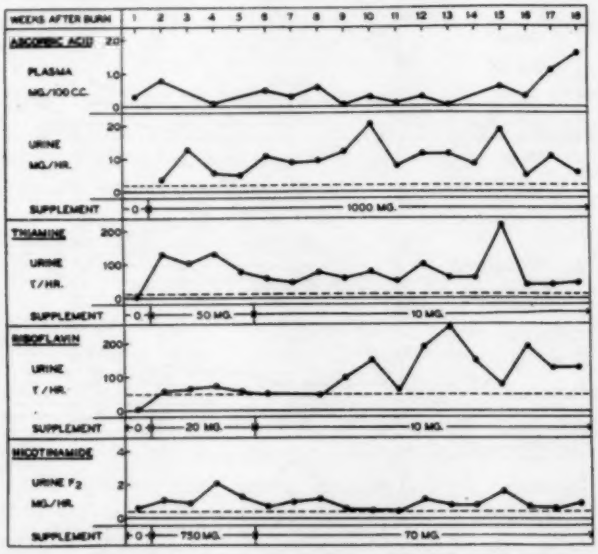

Fig. 6 (case 17).—Plasma ascorbic acid levels and fasting hourly excretion rates of ascorbic acid, thiamine, riboflavin and N-methylnicotinamide in an adult with a minor deep burn complicated by alcoholism and chronic colitis of probable nutritional origin.

were somewhat below the average for normal persons on a nonsupplemented diet. The excretion of N-methylnicotinamide was normal, and the fasting plasma ascorbic acid concentration was 0.3 mg. per hundred cubic centimeters.

From the second through the eighteenth week the patient received 1 Gm. of ascorbic acid daily. The plasma ascorbic acid level varied between 0.1 and 0.8 mg. per hundred cubic centimeters from the second to the ninth week. During the next five weeks the levels varied between 0.0 and 0.3 mg. By the seventeenth week the level had risen to 1.1 mg. and it rose to 1.6 mg. per hundred cubic centimeters in the eighteenth

week. The fasting hourly excretion rate of ascorbic acid varied between 3.8 and 21 mg., with no definite correlation with the plasma vitamin C levels. After the eighteenth week the supplement of ascorbic acid was reduced to 225 mg. daily. The plasma ascorbic acid level fell to 0.6 mg. per hundred cubic centimeters, and the excretion fell to from 0.7 to 2.1 mg. per hour. The fasting hourly excretions of thiamine, riboflavin and N-methylnicotinamide with the patient on the large supplements were well above the average excreted by normal persons on a nonsupplemented diet and comparable to the excretions of normal persons given high supplements.[11]

We believe that the success of the first skin graft in this case, as compared to those in cases 15 and 16, was due to the fact that the

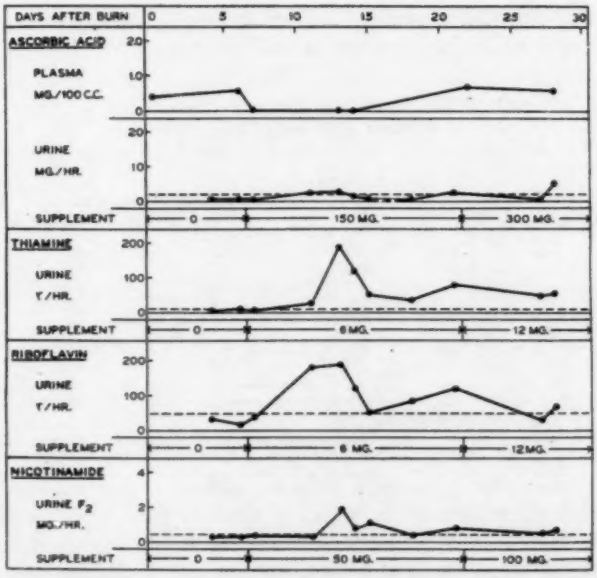

Fig. 7 (case 19).—Plasma ascorbic acid concentration and fasting hourly excretion rate of ascorbic acid, thiamine, riboflavin and N-methylnicotinamide in an adult with an extensive deep dermal burn.

original dietary deficiencies in this patient were completely corrected by the time of grafting while in the other patients the deficiencies had not been corrected.

Severe Burns: Four patients with extensive burns were studied in the early period after injury. In 1 patient (case 18) the burns were almost entirely superficial dermal burns. She was in good nutritional status on entry to the hospital, with a noncontributory past history. Her course was uncomplicated. There were no abnormally low vitamin excretions or fasting plasma ascorbic acid levels. The other 3 patients

had extensive deep dermal or deep burns, and all showed striking abnormalities in vitamin metabolism, as detailed in the following reports.

CASE 19.—J. B., a 42 year old white woman with a noncontributory past history, was admitted to the hospital shortly after receiving flame burns, chiefly deep dermal, of 20 per cent of her body surface and moderately severe damage to the respiratory tract. Examination on admission revealed a fairly well developed and well nourished woman whose systolic blood pressure was 85. She was given plasma and whole blood intravenously. The blood pressure promptly rose to 110 systolic and 70 diastolic and remained satisfactory thereafter. Her temperature rose gradually, reaching a level of 102 F. on the sixth day in the hospital, but fell to 100 F. by the eighth day, at about which level it remained for the next two months. Her appetite was good, and in addition to her food she received protein hydrolysate and dextrose intravenously. Her weight, plasma protein concentration and hemoglobin concentration were maintained.

Most of the burn was extremely deep dermal burn, and it healed slowly, after superficial sloughing, in about nine weeks. Two weeks later, deep phlebitis of the

TABLE 6—*"Low" Saturation Tests of Vitamin Excretions in Four Hours in a Patient Studied (Case 19)**

Day	Ascorbic Acid, Mg.	Thiamine, Mg.	Riboflavin, Mg.	N-Methylnicotinamide, Mg.
0†	28	0.5	1.0	5.4
6	14	1.0	1.0	11.5
13	7	1.0	1.0	5.5
27	58	1.8	0.7	8.0
41	50	3.2	1.2	8.0
48	104	2.1	0.6	10.7
76	60	1.2	0.8	15.9

* The test doses given (intravenously) were: ascorbic acid, 250 mg.; thiamine, 5 mg.; riboflavin, 3 mg., and nicotinamide, 50 mg.
† Day of injury.

right leg and one small pulmonary infarct developed. She recovered from this without further complications in about a week. Skin was grafted over the remaining granulating area on the back in the fourteenth week. A complete take resulted. Her further course was benign, and she was discharged two weeks later. The data on the vitamins are given in charts 7 and 8.

During the first week, the patient received no vitamin supplements. Fasting hourly excretions of thiamine and riboflavin were slightly below the average for normal persons on a nonsupplemented diet. Thereafter she received a supplement of 6 mg. each of thiamine and riboflavin daily for the next two weeks and then 12 mg. daily of each. The fasting hourly excretion levels rose and were within the range of values found for healthy persons receiving large supplements of these vitamins. The excretion of N-methylnicotinamide was about 0.3 mg. per hour during the first week, and it rose thereafter to levels of 0.5 to 1.0 mg. on supplements of 50 to 100 mg. of nicotinamide daily. Results of low saturation tests of thiamine, riboflavin and N-methylnicotinamide performed on the first, sixth, thirteenth, twenty-seventh,

forty-first, forty-eighth and seventy-sixth day were essentially normal except for a slightly low excretion of thiamine on the first test. Table 6 gives the results of these tests.

During the first week, no supplement of ascorbic acid was given. The plasma level, which was 0.4 mg. per hundred cubic centimeters on the first day, fell to zero by the seventh day. Fasting hourly excretions during this week were also low, averaging about 0.6 mg. Saturation tests, with 250 mg. of ascorbic acid as the test dose, performed on the day of entry and again on the sixth day after entry revealed plasma levels and excretion values which were considerably lower than normal and in fact, similar to those seen in patients with scurvy. During the second and third weeks, the patient received a supplement of 150 mg. of ascorbic acid daily. The plasma vitamin C concentration remained exceedingly low. The rate of fasting hourly excretion rose during the second week to 2.2 mg. and then fell again to 0.8 mg. during the third

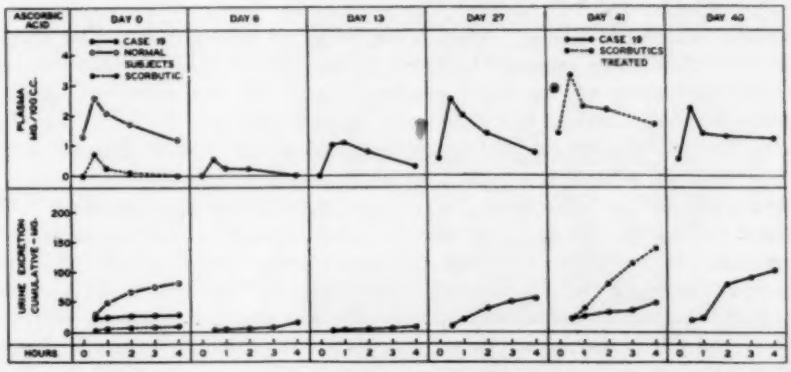

Fig. 8 (case 19).—Serial ascorbic acid saturation tests in an adult with extensive deep dermal burn. The test dose was 250 mg. given intravenously.

week. A saturation test with the same dose of ascorbic acid performed on the thirteenth day showed an even lower four hour excretion, only 7 mg. being excreted. By the twenty-seventh day the excretion rose to 50 mg., which is the average amount excreted by normal persons on a non-supplemented diet. During the fourth week, the patient received a supplement of 300 mg. of ascorbic acid a day. On this regimen the plasma ascorbic acid rose to 0.6 mg. per hundred cubic centimeters and the fasting hourly excretion to 2.7 mg. The four hour excretion rate and the plasma ascorbic acid levels after the injection of test doses also rose during this period. However, even after a daily supplement of 300 mg. of ascorbic acid had been given for twenty days the plasma levels and the excretion rates were lower than the average observed in patients with scurvy who had received a daily supplement of 250 mg. for twelve days.

CASE 20.—J. R., a 27 year old white man, was admitted to the hospital shortly after receiving extensive flame burns involving 40 per cent of the body surface, the burn being chiefly deep. For the year or two prior to his entry he had been drinking large amounts of alcohol but apparently had also been eating fairly well. Examination revealed a well developed, apparently fairly well nourished man who was somewhat disoriented and delirious. On entry the blood pressure was 90 systolic and 70 diastolic and the pulse was of good quality. The blood pressure and the pulse thereafter were normal, and there was no period of shock. During the first twenty-four hours he received 3,750 cc. of plasma and 5 liters of other fluids intravenously, chiefly isotonic solution of sodium chloride. The urine output during the first twelve hours was 1,000 cc.

Shortly after entry the patient went into delirium tremens, the temperature having risen to 105.6 F. rectally on the second day. The respirations at this time were 45, and the pulse rate was 145. He was given large amounts of vitamins (details of vitamin therapy are given later), paraldehyde and intravenously administered amigen, dextrose and isotonic solution of sodium chloride. He was also given a high protein, high caloric intake by mouth and by intubation. The delirium tremens was finally controlled after five days. The temperature continued to be elevated, reaching 104.5 F. rectally. The respirations fluctuated between 30 and 50 and were occasionally labored. He was coughing and raising thick yellow sputum. The chest could not be examined satisfactorily by either physical or roentgenologic examination because of the burns and dressings. He was given full doses of sulfadiazine (6 Gm. a day) and 20,000 units of penicillin intramuscularly every two hours. Two weeks after entry he was placed in an oxygen tent for possible cooling effects and in an attempt to relieve some of the respiratory distress.

His condition gradually became worse, and three weeks after his entry to the hospital the temperature rose suddenly to 108 F. and he became comatose. The respirations were shallow and rapid, his pupils were unequal in size and there appeared to be slight facial weakness on the right side. The neurologic consultant suggested the possibility of a brain abscess. He was sponged vigorously with cold alcohol, and the temperature dropped to 104 F. However, he gradually became weaker and died on the following day.

During the first five days, there had been moderate negative nitrogen balance; thereafter, his intake of nitrogen was gradually increased and reached a level of about 40 Gm. a day by the ninth day. At this time his caloric intake was 3,500. There was then slight apparent positive nitrogen balance. This high intake of nitrogen continued until the twenty-first day, when his intake diminished to less than one half of this amount, and there was slight negative balance again.

The plasma protein concentration was 3.5 Gm. per hundred cubic centimeters on the first day, with an albumin level of 2 Gm. This rose gradually to a level of 5.0 Gm. on the tenth day, but the albumin remained at 2.1 Gm. The plasma protein concentration on the twentieth day was 5.4 Gm. His hemoglobin content, which had been 119 per cent on entry, fell to 64 by the tenth day and thereafter ranged between 62 and 79 per cent. He was given multiple transfusions of 500 cc. of whole blood.

Studies of vitamin excretion were not done. He received an average of 50 mg. of thiamine, with extremes of 20 to 60 mg., 20 mg. of riboflavin, with extremes of 10 to 40 mg., and 500 mg. of nicotinamide, with extremes of 100 to 800 mg., daily after the first day, chiefly by the intramuscular route. The lower doses in each instance were given from the sixth to the eleventh day. Fasting plasma ascorbic acid concentrations were measured, and the data are given in chart 9.

During the first five days the patient was given an average of 1 Gm. of ascorbic acid intramuscularly daily. During this time the plasma ascorbic acid concentration ranged from 0.3 to 0.7 mg. per hundred cubic centimeters. From the sixth to the twelfth day he was given an average of 500 mg. of ascorbic acid intramuscularly and 225 mg. orally. During this time the plasma ascorbic acid concentration fell, being zero on the eleventh day. Therefore he was given 2 Gm. intramuscularly daily as well as 225 mg. by mouth. It was only after two days of this high intake that a measurable amount of ascorbic acid appeared in the plasma. This indicates that the patient's store had become markedly depleted during the preceding week despite the fact that he had been given a supplement of 750 mg. of ascorbic acid daily.

CASE 21.—J. V., a 35 year old white man with a noncontributory past history, was admitted to the hospital shortly after receiving flame burns, chiefly deep, involving 40 per cent of his body surface. The accident occurred when he fell asleep smoking a cigaret while intoxicated. Examination on entry revealed him

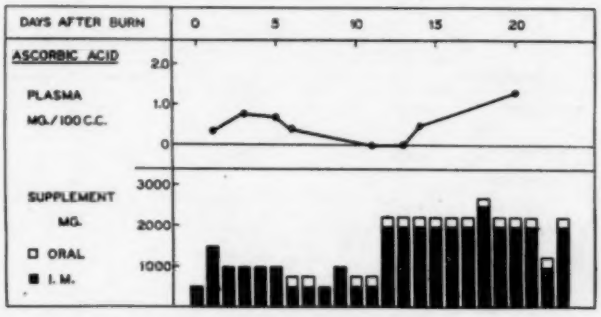

Fig. 9 (case 20).—Nitrogen balance and plasma ascorbic acid concentration in an adult with an extensive fatal deep burn.

to be well developed and well nourished. During the first day he was given 1,700 cc. of plasma, 2,400 cc. of blood, 3,000 cc. of isotonic solution of sodium chloride and 500 cc. of dextrose in water intravenously. In addition, 1,000 cc. of isotonic solution of sodium chloride and 500 cc. of dextrose in water were given by clysis, and 4,000 cc. of water containing dextrose and sodium bicarbonate was given by mouth. His urine output was low the first day but normal thereafter. He was never in shock. A dry sterile pressure dressing was applied shortly after his entry to the hospital, without preliminary cleansing or débridement. During the first week, his temperature ranged between 101 and 103 F. rectally. Administration of penicillin in doses of 15,000 units intramuscularly every three hours was begun on the third day. He was given amigen and dextrose intravenously and amigen, "nutramigen" and dextrose by intubation. The average daily intake was 150 Gm. of protein, and his total nourishment represented 3,000 calories. The daily urinary nitrogen output during this time averaged about 19 Gm. His weight at the end of the first week was 163 pounds (74 Kg.), his preadmission weight having been 155 pounds (70 Kg.). He did not appear edematous at this time. The blood nonprotein nitrogen level and the urine output were normal. The plasma protein

concentration fell from a level of 5.8 to 4.7 Gm. and the albumin from 4.1 to 3.3 Gm. His hemoglobin content was 85 per cent.

The first dressing was done on the morning of the eighth day. Dry adherent slough was present over most of the burned areas. There was no surrounding redness, swelling or tenderness. A dry pressure dressing was reapplied. Six hours later he was much sicker. His temperature had risen to 104 F. rectally; the pulse rate was 140 and the respirations 25. He was irrational. The dose of penicillin was increased to 20,000 units every two hours. The following morning the temperature had risen still further to a level of 108 F. and the pulse rate to 160. The respirations remained at 28 but were somewhat shallow. He had a

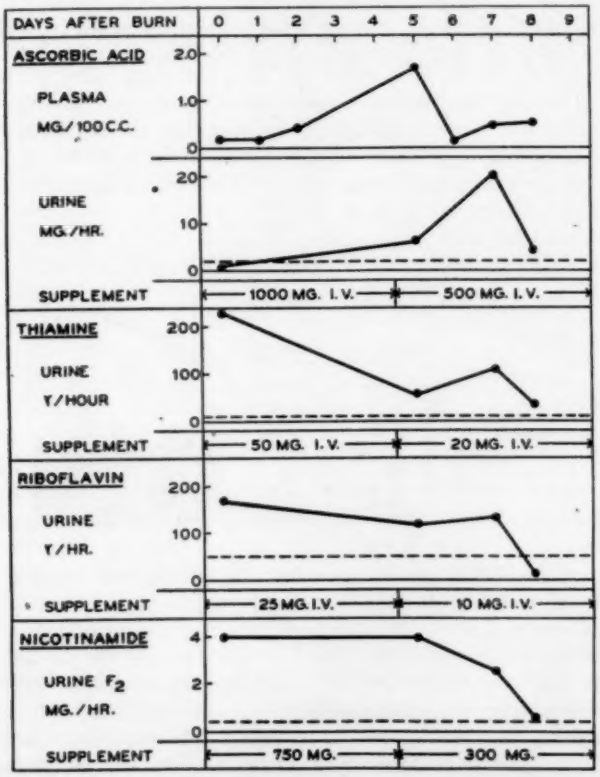

Fig. 10 (case 21).—Plasma ascorbic acid concentration and fasting hourly excretion rates of ascorbic acid, thiamine, riboflavin and N-methylnicotinamide in an adult with an extensive fatal deep burn.

moderate nonproductive cough. Continuous sponges with iced alcohol were started, and sulfadiazine was given. He was placed in an oxygen tent. The temperature came down to 104 F. and the pulse rate to 130 within a few hours, but the following day the temperature rose again, this time to a level of 109 F., and the patient died shortly thereafter.

The data on the vitamins are shown on chart 10.

During the first five days the patient was given a daily supplement of 1,000 mg. of ascorbic acid, 50 mg. of thiamine, 20 mg. of riboflavin

and 750 mg. of nicotinamide. The fasting hourly excretion rates on the first day were normal for thiamine, riboflavin and nicotinamide but slightly low for ascorbic acid. Determinations after the fifth day showed levels which were all above the average for healthy persons on a normal diet but seemed low for the large dosage which the patient was receiving.

The level of plasma ascorbic acid two hours after the burn and before any additional ascorbic acid was given was 0.16 mg. per hundred cubic centimeters. Ten hours later, seven hours after 1 Gm. had been given intravenously, this level was unchanged. Twelve hours later, fifty minutes after another gram had been given intravenously, the level was 2.08 mg. By the fifth day the fasting plasma ascorbic acid level had risen to 1.70 mg. per hundred cubic centimeters, the patient having received 1 Gm. of ascorbic acid daily. Therefore, with a supplement of 500 mg. daily the ascorbic acid level fell to 0.2 mg. on the sixth day and 0.5 mg. on the seventh and eighth days. These values are considerably lower than those observed in normal persons receiving 500 mg. of ascorbic acid daily.

COMMENT

The data presented demonstrate that after severe burns there are considerable alterations in the metabolism of ascorbic acid, thiamine, riboflavin and nicotinamide, as evidenced by a low concentration of ascorbic acid in the plasma either with the patient fasting or after saturation tests and low urinary excretion of these vitamins either with the patient fasting or after the injection of test doses. The extent of the abnormalities paralleled the severity of the burn. Patients with burns, minor in extent and superficial in depth, did not show these changes unless there was in addition some complicating factor such as preexisting deficiency, low intake of food or serious infection. In contrast, patients with extensive deep burns invariably showed notable abnormalities. These changes were greatest in the early period following injury but continued in some cases far into the chronic stage. In this respect, the upset in vitamin metabolism parallels the upset in nitrogen metabolism which follows burns.[15]

The following factors must be considered in an attempt to account for the findings.

1. *Preexisting Deficiency.*—Three patients gave evidence on entry to the hospital of possible vitamin deficiency. One (case 15) was a previously healthy young woman whose diet was adequate except for lack of citrus fruits. There were no stigmas of ascorbic acid deficiency

15. Taylor, F. H. L.; Davidson, C. S.; Levenson, S. M., and Adams, M. A.: Abnormal Nitrogen Metabolism in Patients with Thermal Burns, New England J. Med. **229**:855-859, 1943.

on admission. Her burn was minor. She remained on a diet low in vitamin C for six weeks, and during this time the fasting hourly excretion rate of ascorbic acid and the fasting plasma ascorbic acid concentrations were low. The excretion of the other vitamins was normal. A skin graft at this time failed. Thereafter she received a supplement of 1 Gm. of ascorbic acid daily, and the plasma vitamin C level and the urinary excretion rose to normal. A skin graft at this time was completely successful.

Another patient who entered the hospital with probable preexisting vitamin deficiency was the patient in case 17, a 60 year old man who for a period of six months prior to entry ingested a poor diet and large quantities of alcohol and suffered from intermittent bloody diarrhea. On entry to the hospital he was moderately underweight, but there were no definite stigmas of specific vitamin deficiency. His burn was of moderate severity. During the first week, the urinary excretions of thiamine, riboflavin and n-methylnicotinamide were low (excretion of ascorbic acid not measured) and the fasting plasma ascorbic acid levels were also low. Thereafter he was given large daily supplements of all vitamins, and the urinary excretions of the four vitamins and the plasma ascorbic acid concentration rose to normal levels. The third patient who entered the hospital with probable preexisting nutritional deficiencies, although none were apparent on entry, was the patient in case 20. He was a 27 year old man who had had alcoholism for the year previous to injury. Despite a daily supplement of 750 mg. of ascorbic acid daily, chiefly by the intramuscular route, his plasma ascorbic acid concentration fell to zero in the second week and remained at this level even after 4 Gm. of ascorbic acid had been given in two days. This would indicate that some factor in addition to possible preexisting deficiency was present in this patient, since the experiments of Crandon, Lund and Dill [16] showed a much more rapid rise in the plasma ascorbic acid after actual scurvy had been treated with comparable amounts of vitamin C. In the other cases studied preexisting deficiency did not play an important role.

2. *Inadequate Dosage.*—In a few patients the intake of the various vitamins was probably low and may have accounted in part for the finding of low excretion values. However, in the patients with the most pronounced abnormalities the actual intake of vitamins was extremely high—far above the so-called optimum amount for healthy persons.

3. *Failure of Absorption.*—Failure of absorption can be ruled out by the fact that in the most severely burned patients, who showed the

16. Crandon, J. H.; Lund, C. C., and Dill, D. B.: Experimental Human Scurvy, New England J. Med. **223**:353-369, 1940.

most striking changes, the vitamins were given slowly by intravenous or intramuscular routes.

4. *Excretion in Sweat.*—Sargent, Robinson and Johnson [17] have shown that significant quantities of these vitamins are not lost by this route even under conditions of extreme sweating.

5. *Excretion in Edema Fluid or into the Exudate from the Burned Surfaces.*—Andreae and Browne [6] have shown that the concentration of ascorbic acid in the early edema fluid of burns is similar to the concentration in the blood plasma. They expressed the opinion that diversion of ascorbic acid into the edema fluid cannot account for the changes in the metabolism of ascorbic acid observed. The amounts of other vitamins excreted in the early edema fluid or of all the vitamins excreted in the later exudate have not been determined. However, the excretion in the exudate cannot explain the early findings, since during the first week the external exudation from deep burns is minimal and it is the patients with deep burns who demonstrate the most appreciable changes. On the other hand, it may account in part for the findings in the later stages of the injury.

6. *Storage.*—As noted in the beginning, Andreae and his associates interpreted the evidence from their studies as indicating that riboflavin is stored early after injury and excreted later while in the case of ascorbic acid there is no evidence for storage, since the early "retention" was not followed by a period of increased excretion. There are no data in the present study which would suggest an early storage, but it is possible that such could not be demonstrated by the technics used.

7. *Excretion of the Vitamins in Forms Other Than Those Measured.*—Thiamine and nicotinamide are excreted in a multiplicity of forms, and it is possible that determinations of the excretion of only one of the forms does not give a true picture of the metabolism of these vitamins. Ascorbic acid is excreted in normal persons chiefly in the reduced form, but a small proportion is excreted in the reversibly oxidized or dehydro form. Andreae and Browne [6] found no disproportionate amount of dehydroascorbic acid in the urine of burned patients. On the other hand, an increased proportion of dehydroascorbic acid has been reported in the adrenals of burned animals.[18] Whether ascorbic acid may be excreted in other forms, such as the irreversibly oxidized form, is not known. Riboflavin, as far as is known, is excreted as such.

8. *Destruction.*—It is possible that the vitamins may be destroyed in the burned patients without any useful function being performed

17. Sargent, F.; Robinson, P., and Johnson, R. E.: Water Soluble Vitamins in Sweat, J. Biol. Chem. **153**:285-294, 1944.

18. Voronoy and Lipovetska: Eksper. med. **4**:1, 1940; cited by Greig, M. E., and Govier, W. M.: Studies on Shock Induced by Hemorrhage, J. Pharmacol. & Exper. Therap. **79**:169-175 (Oct.) 1943.

during their destruction. This study contributes no evidence for or against such a postulate.

9. *Increased Utilization.*—It has been shown in recent years that many of the vitamins play more fundamental roles than merely the prevention or curing of the well known deficiency syndromes such as scurvy, beri-beri and pellagra. Thiamine, riboflavin and nicotinic acid are concerned with the enzyme systems that control carbohydrate metabolism, and in addition riboflavin is important in amino acid metabolism. Ascorbic acid has been shown to have a fundamental role in the formation of the adrenocortical hormone [19] and in general tissue metabolism. These functions indicate that the four vitamins play important roles in connection with recovery from hemorrhagic shock,[20] injury and acute infections,[21] since disturbances in the metabolism of carbohydrate,[22] protein and adrenocortical hormones are found in these conditions. Thus, Govier [23] has found that the mortality of normal dogs exposed to a standardized type of hemorrhagic shock was reduced when thiamine was given in large doses before or after bleeding. In addition, dogs deficient in thiamine were particularly susceptible to death from hemorrhagic shock. Holt [24] has demonstrated apparent increased utilization of thiamine in conditions of stress such as increased basal metabolism and fever. On the other hand, Bergman and others [25] were unable to show any beneficial effect of thiamine or ascorbic acid used alone as sole therapeutic measures in the treatment of shock due to scalding burns in mice. In the later period of burns, when epithelization and formation of granulation tissue are taking place, it is probable that there is an increased demand for ascorbic acid and riboflavin and possibly for other vitamins.

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19. Sayers, G.; Sayers, M. A.; Liang, T., and Long, C. N. H.: The Effect of Pituitary Adrenotropic Hormone on the Cholesterol and Ascorbic Acid Content of the Adrenal of the Rat and the Guinea Pig, Endocrinology **38**:1-9, 1946.

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22. Aub, J. C., and Wu, H.: Studies in Experimental Traumatic Shock: III. Chemical Changes in Blood, Am. J. Physiol. **54**:416 (Dec.) 1920.

23. Govier, W. M.: Rationale for Use of Vitamins in the Therapy of Shock and Anoxia, J. A. M. A. **126**:749-750 (Nov. 18) 1944.

24. Holt, L. E., Jr.: The Thiamin Requirement of Man, Federation Proc. **3**:171-178, 1944.

25. Bergman, H. C.; Rosenfeld, D. D.; Hechter, O., and Prinzmetal, M.: Ineffectiveness of Adrenocortical Hormones, Thiamin, Ascorbic Acid, Nupercaine, and Post Traumatic Serum in Shock Due to Scalding Burns, Am. Heart J. **29**:506-512 (April) 1945.

SUMMARY AND CONCLUSIONS

The data presented should be considered to indicate, as a first approximation, that large doses of ascorbic acid, thiamine, riboflavin and nicotinamide are needed by severely burned patients and that some supplementation at a lower level is needed for many patients with burns of moderate extent. A similar conclusion has been reached in a study of patients with hemorrhagic shock, traumatic injuries and infection.[26]

It is suggested that 1 to 2 Gm. of ascorbic acid, 10 to 20 mg. each of thiamine and riboflavin and 150 to 250 mg. of nicotinic acid be given daily to severely burned patients and that the doses may be needed for long periods. However, these vitamins alone will not satisfy the nutritional needs of the patient, which include a high protein, high carbohydrate diet and ample quantities of yeast, crude liver extract (given orally) and vitamins A and D.

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26. Levenson, S. M.; Green, R. W.; Taylor, F. H. L.; Robinson, P.; Paige, R. W.; Johnson, R. E., and Lund, C. C.: Ascorbic Acid, Riboflavin, Thiamin, and Nicotinic Acid in Relation to Severe Injury, Hemorrhage, and Infection in the Human, Ann. Surg. **124**:840-856, 1946.

ALUMINUM HYDROXIDE AND MAGNESIUM TRISILICATE PLUS MUCIN IN TREATMENT OF PEPTIC ULCER

Gastroscopic and Clinical Studies

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CLINICAL study has shown that antacids are the most important single factor in controlling gastric pain and discomfort due to hyperacidity and peptic ulcer. A review of medical literature and advertisements by pharmaceutic companies reveals that physicians have been led to believe that antacids, especially aluminum gels and magnesium trisilicate, have an astringent and protective coating action on the gastric mucosa. There has been no definite proof brought forward to substantiate or refute the suggestion that aluminum gels have an astringent or coating effect on the mucosa of the stomach.

Ivy and his associates [1] have called attention to the fact that the aluminum combines with the gastric mucus to form a flaky precipitate, which adheres to the mucosa of the stomach and duodenum. A film of this nature would serve as a physical protection to the mucosa and exert an antacid action as well. In animals that had received the aluminum preparations for some time, they observed at autopsy that the folds of the mucosa in the stomach and duodenum were covered with flaky curds, presumably precipitated mucus. At times the duodenum was so coated that about two thirds of the mucosa appeared as if it had been covered with flour paste.

Fogelson [2] in 1931 was the first to advocate gastric mucin in the treatment of peptic ulcer. This treatment met with disfavor chiefly because of its nauseating taste and because the commercial products at that time contained histamine in such quantities as to increase decidely the gastric acidity.

Fogelson [3] also showed that mucin had a retarding effect on pepsin activity.

From the Department of Medicine, Loyola University School of Medicine.

1. Ivy, A. C.; Terry, L.; Fauley, G. B., and Bradley, W. B.: Am. J. Digest. Dis. **3**:879, 1937.

2. Fogelson, S. J.: Treatment of Peptic Ulcer with Gastric Mucin, J.A.M.A. **96**:673 (Feb. 28) 1931.

3. Fogelson, S. J.: Illinois M. J. **62**:516, 1932.

Jones,[4] as well as many other authors, claimed that the beneficial effects of the aluminum hydroxide gels are largely the result of their astringent action. Page and Thomas [5] observed that magnesium trisilicate acquires gelatinous consistency in the presence of acid and if it lodges in the ulcer crater will progressively neutralize the acid which diffuses through it.

We have gastroscopically observed the physical appearance in the stomach of four of the well known proprietary aluminum gels, of magnesium trisilicate and of calcium carbonate. Thirty-five patients were used in this study—in 15 the stomach had been previously diagnosed as normal, 3 had been given a diagnosis of hypertrophic gastritis, 5 atrophic gastritis, 9 duodenal ulcers and 3 gastric ulcers. The patients were without food for twelve hours prior to gastroscopy. The gastric contents were aspirated in all but 10 of the patients before instillation of the antacid, in order to remove any stomach contents that might still be present after the twelve hour fast. The antacids were given in half ounce doses five, fifteen, thirty and forty-five minutes, respectively, prior to gastroscopy.

There was no essential difference in the appearance of the antacids in those patients in whom the gastric contents were aspirated and in those in whom aspiration was not done. From five minutes to half an hour after instillation the antacid appeared as a large white irregular mass or broken up into smaller clumps and scattered irregularly throughout the stomach. The speed with which the antacid left the stomach was variable. At the end of twenty to forty-five minutes we frequently noted, especially when liquid preparations were used, that there was a total absence of antacid in the stomach. This observation was confirmed by roentgenologic studies in which we added sufficient barium sulfate to the liquid antacid preparations to visualize the antacid. Roentgenograms were taken at twenty minute intervals, and it was noted in some instances that the barium sulfate antacid preparation was absent at the end of forty minutes (fig. 1). The antacids, as seen gastroscopically, were scattered throughout the stomach in clumps of various sizes and could not be differentiated one from the other. We did not get the impression that any of the antacids employed in this study had a distinct coating effect. In a few instances in which there was an increase of mucus in the stomach, there seemed to be a slight tendency for the aluminum gels to diffuse through the mucus which adhered to the walls of the stomach.

In 3 of the patients in whom aspiration had not been done and in 5 in whom aspiration had been done prior to gastroscopy and to instillation of the antacid, there was considerable mucus present in the

4. Jones, C. R., Jr.: Pennsylvania M. J. **43**:468, 1940.
5. Page, R. C., and Thomas, E. G.: Mil. Surgeon **85**:307, 1939.

stomach. The aluminum gels seemed to diffuse through the mucus and appeared to be suspended in a finely divided state, clinging or adherent to the mucosa in thick strings which extended from the anterior and posterior walls of the stomach. Increased amounts of mucus appeared to delay the exodus of aluminum gels from the stomach. With small amounts of mucus there was no essential difference in the physical properties of the calcium carbonate, magnesium trisilicate or aluminum hydroxide.

Our observations gastroscopically substantiated those of Ivy and his associates and led us to the conclusion that a coating effect is obtained only when sufficient gastric mucus is present to allow the aluminum gels or magnesium trisilicate to diffuse through it and remain clinging to the walls of the stomach in a filmlike coating. We inferred from this

Fig. 1.—Roentgenogram of the stomach twenty minutes after ingestion of barium sulfate plus aluminum hydroxide with magnesium trisilicate gel. The stomach is empty at the end of forty minutes.

that there should be a combination of aluminum gels and/or magnesium trisilicate, with gastric mucin, in order to insure a sufficient amount of mucoid substance in the stomach when the antacid is instilled. In the presence of a sufficient amount of gastric mucin, aluminum gels and magnesium trisilicate tend to diffuse through the gastric mucin and in that manner produce a protective coating action.

We then decided to study in a similar manner, gastroscopically and roentgenologically, the physical appearance of a mixture containing magnesium trisilicate and aluminum hydroxide, to which was added from 10 to 20 per cent of gastric mucin.[6] Three patients with gastric

6. The preparations used were palatable and free from secretagogue action.

ulcer, 5 with atrophic gastritis and 11 with normal stomachs were used for this purpose. Gastroscopic observations were made before the instillation of this mixture and again twenty minutes to an hour and a half after the mixture was instilled. A vegetable dye was added to the mixture in several instances as a further means of identification and assurance that the physical appearance of the mixture was not due to the presence of normal gastric mucus.

The mucin antacid mixture was administered in the form of a palatable powder or tablet, thoroughly chewed and swallowed without the use of water. Gastroscopic observations were made at intervals of half an hour to an hour and a half after instillation of the mucin antacid. Invariably we were able to demonstrate a decided tendency toward

Fig. 2.—Roentgenogram of the stomach twenty minutes after ingestion of barium sulfate plus mucin antacid mixture. The mixture is still present at the end of one hour and forty minutes.

coating and filming of the mucosa. Our most striking results were obtained in the patients suffering from gastric ulcer. The ulcer crater in each instance was covered by a pool of the antacid mixture, and the mucosa surrounding the ulcer had a thick filmy coating. The mucin antacid was observed gastroscopically to be present in the stomach as long as an hour and forty minutes after instillation. This we confirmed roentgenologically by adding barium sulfate to the mixture and taking roentgenograms at twenty minute intervals (fig. 2).

This mucin antacid mixture has been tested for its effect on gastric acidity and has been compared with two currently used aluminum gel preparations and a powder containing calcium carbonate and sodium

bicarbonate.[7] It appears that this mucin antacid has almost a sodium-bicarbonate-like rapid effect on the gastric acidity, which lasts for about half an hour, and then the gastric acidity seems to return gradually to its former level. This return is less rapid and less steep than that following ingestion of the powders used in the Sippy treatment.[8] When compared with an alumina product, it induces a much more rapid response. At the end of an hour the gastric acidity has almost reached the control day level (fig. 3).[7]

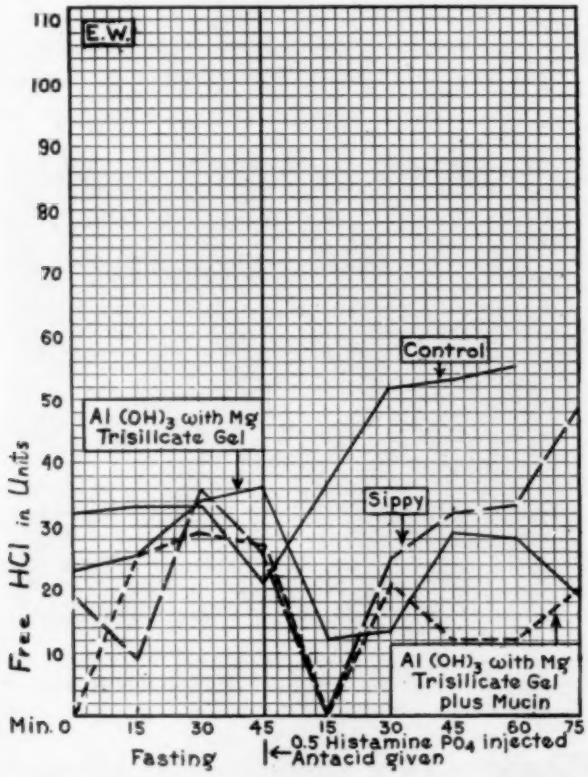

Fig. 3.—Chart showing effect on gastric acidity of aluminum hydroxide with magnesium trisilicate gel, of aluminum hydroxide with magnesium trisilicate gel plus mucin and of powders used in the Sippy treatment [8] as compared with the control day level.

The retardation of the action of pepsin on frog muscle by gastric mucin was studied. Pepsin in concentrations of 5.0 mg and 10.0 mg. per

7. Steigmann, F., and Kammerling, T. S.: Personal communication to the authors.

8. In the Sippy treatment powder containing 10 grains (0.65 Gm.) each of heavy calcined magnesia and sodium bicarbonate is alternated with powder containing 10 grains of bismuth subcarbonate and 20 or 30 grains (1.3 to 1.9 Gm.) of sodium bicarbonate.

hundred cubic centimeters, in both 0.2 per cent and 0.3 per cent hydrochloric acid, causes complete digestion of muscle tissue of the leg of a frog. Retarding action of gastric mucin is more apparent in pepsin solutions in 0.2 per cent hydrochloric acid than in equally concentrated pepsin solutions in 0.3 per cent hydrochloric acid, although the difference is not great. The retarding action of gastric mucin in these experiments confirms the observations of Fogelson.

Thirty-four patients with peptic ulcer have to date been tested clinically with this new mucin antacid preparation. The test periods varied from four to twelve weeks. The mixture has been administered in tablet form, thoroughly chewed, or powder form and given at one to two hour intervals. All the patients have been promptly relieved of their symptoms and are progressing clinically. It is, of course, necessary to follow these patients for many months until a definite conclusion as to the clinical results can be made. However, the preliminary observation points to a satisfactory response. In 2 patients with large gastric ulcers, observed gastroscopically and roentgenologically, the ulcers were completely healed at the end of six weeks.

It is our belief that the addition of mucin to a mixture of aluminum hydroxide and magnesium trisilicate, administered in the form of a powder or tablet (thoroughly chewed) offers a distinct advantage in the treatment of peptic ulcer for the following reasons: (1) A distinct coating action is obtained; (2) pepsin activity is retarded; (3) gastric acidity is readily neutralized without the dangers of alkalosis, and (4) the exodus of the mucin mixture from the stomach is delayed.

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NEWER ASPECTS OF BENIGN TUMORS OF THE BREAST

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BENIGN tumefactions of breast tissue and its integument may be divided into: A. Mammary dysplasia, resulting from abnormalities in the secretion of the ovarian hormones. This is exemplified by:

(1) Mastodynia—painful mammary tissue of increased density.

(2) Adenosis—nodosities from epithelial hyperplasia with small cysts.

(3) Cystic disease—one or more cysts of appreciable size resulting from secretory changes.

B. Benign neoplasia, characterized by true benign tumor formations. Examples of this are:

(1) Benign fibroadenoma with a structure of fibrous tissue and ducts.

(2) Benign intracystic papillomas, which include (1) papillary invaginations of larger ducts, (2) intracystic papillomas and (3) papillary hyperplasia which occurs in adenosis of the breast.

(3) Benign nonindigenous tumors of the breast, involving (*a*) fat (lipoma and xanthoma), (*b*) lymphatic vessels (angioma, lymphangioma and lymphoma), (*c*) muscles (leiomyoma and myoblastoma), (*d*) skeletal mesenchyme (chondroma and osteoma) and (*e*) skin appendage (dermoid cysts and sweat gland tumors).

This classification is taken from that of Geschickter and is considered to be extremely practical.

This paper is concerned with benign tumefactions of the breast proper, namely, mammary dysplasia and mammary neoplasia (benign).

A. MAMMARY DYSPLASIA

Mammary dysplasia is neither inflammatory nor neoplastic but represents an expression of ovarian dysfunction in menstruating women. This point of view has not gone unchallenged. Taylor [1] and Friedman and

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1. Taylor, H. C., Jr.: The Evidence for an Endocrine Factor in the Etiology of Mammary Tumors, Am. J. Cancer **27**:525, 1936; The Endocrine Aspects of Chronic Mastitis, Surg., Gynec. & Obst. **74**:326, 1942.

others [2] in independent studies concluded that dysplasia was related to ovarian dysfunction in some cases, but they felt that this condition must be referred to a variety of factors, among which the nervous disturbances depending mainly on pelvic disorders were prominent. Ewing,[3] from a review of the literature and from his own observations, concluded that mammary dysplasia (chronic cystic mastitis) has notably a hereditary character, the main etiologic factor residing in the intrinsic character of the breast itself influenced more or less by hormonal, nervous and local conditions.

Bucher and Geschickter,[4] however, have followed patients intensively by doing endocrine assays on total collections of the daily urine through one or more menstrual cycles. Both estrogen and pregnandiol (an index of corpus luteum function) were assayed. The results of these studies together with the results of experimental studies by Geschickter and others on the production of mammary dysplasia, mammary neoplasia, and cancer resulting from prolonged overstimulation with estrogen strongly support ovarian dysfunction as a principal cause.

Estrogen in varying dosages combined with other hormones which produce lobule formation appears to produce experimentally changes in animals simulating the various changes seen in chronic cystic mastitis.

Many observers [5] support a definite endocrine factor as being linked with mammary dysplasia, benign mammary neoplasia and the production of carcinoma of the breast.

Mastodynia.—Mastodynia is common in women between the ages of 20 and 40 years. Married women who become affected predominate over unmarried women in the ratio of 3 to 1. It is characterized by pain, which is gradual in onset over a period of months. The pain is

2. Friedman, M.; Finkler, R., and Antopol, W.: The Relation of Ovarian Hormones to Benign Breast Hyperplasia and Neoplasia, Radiology **33**:725, 1939.

3. Ewing, J.: Hormonal Relations of Chronic Mastitis, in Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1940, p. 538.

4. Bucher, N., and Geschickter, C. F.: Corpus Luteum Studies: I. Recovery of Pregnandiol from Urine, Endocrinology **27**:727, 1940; II. Pregnandiol and Estrogen Output in the Urine of Patients with Chronic Cystic Mastitis, J. Clin. Endocrinol. **1**:58, 1941.

5. (*a*) Geschickter, C. F.: Chronic Cystic Mastitis or Mammary Dysplasia, in Diseases of the Breast, Philadelphia, J. B. Lippincott Company, 1945, pp. 183-260. (*b*) Astwood, E. B., and Geschickter, C. F.: Changes in the Mammary of the Rat Produced by Various Glandular Preparations, Arch. Surg. **36**:672 (April) 1938. (*c*) Bonser, G. M.: The Effects of Estrone on the Mammary Gland of Male Mice, in Second International Congress Against Cancer, 1937, p. 53. (*d*) Gardner, W. U.: Influence of Oestrogenic Hormones on Abnormal Growth, in Ward, H. B.: Some Fundamental Aspects of the Cancer Problem, American Association for the Advancement of Science, New York, The Science Press, 1937, p. 67. (*e*) Nathanson, I. T.: The Relation of Hormones to Diseases of the Breast, Surgery **16**:108, 1944. (*f*) Bucher and Geschickter.[4]

worse in the premenstruum and is referred to a portion of the breast (usually the outer and upper third) which is more tender, firmer, thicker and more granular than the surrounding breast. It may be unilateral or bilateral.

The patients may fall into two endocrine groups:

(1) Women in the childbearing age who have a tendency toward sterility and who have not been recently pregnant. The breasts are well developed, the menstrual history is normal and the disturbance in the breasts comes late after maturity and is usually transient.

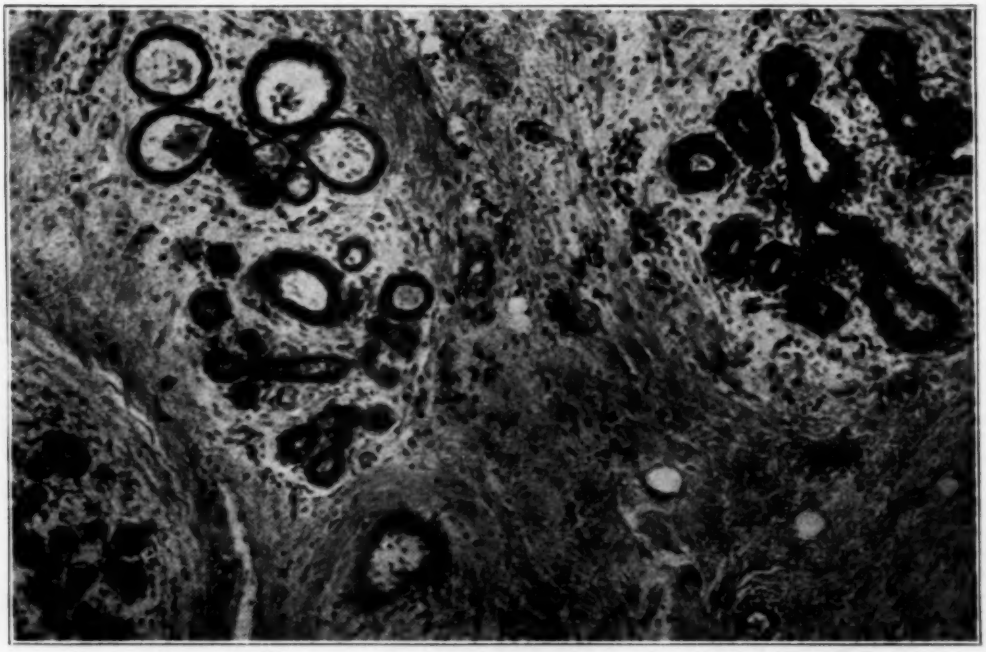

Fig. 1.—Photomicrograph of typical mastodynia tissue. (All illustrations except figures 2 and 3 by courtesy of Dr. C. F. Geschickter and the J. B. Lippincott Company, from Diseases of the Breast, Philadelphia, J. B. Lippincott Company 1943).

(2) Young childless women with small atrophic breasts. The menses are irregular, and they are frequently sterile. Pelvic inflammatory disease is not infrequently encountered. The breasts suggest a primary mammary deficiency dating from shortly after adolescence.

The fear of cancer in the mind of the patient or of the physician has afforded many pathologic specimens to be observed. Grossly, the tissue is nonencapsulated, dense and fibrous. Small cysts may be present. Histologically (fig. 1) there is imperfect lobule formation and an increase in periductal and intralobular stroma. Irregular epithelial growth is noted in the terminal tubules, which may be dilated

The defective lobule formation, as demonstrated in recent studies,[5a] is due to reduced function of the corpus luteum, which in some patients may be a relative lowering of the function or excessive stimulation by the estrogenic hormone. Normal lobule formation is dependent on the proper ratio of estrogen and luteal hormones.

Treatment: The treatment of mastodynia is varied. Once the diagnosis of cancer or true infection has been ruled out, simple supportive measures are worth while, including reassurance and a breast support (brassiere). Estrogen in doses of 10,000 international units intramuscularly once a week between two periods and then 2,000 units once a month in the premenstruum for a limited time has proved effective in controlling the condition. Testosterone propionate in doses of 25 mg. per week for a short while has proved satisfactory in a few cases. Progesterone therapy has proved to be the treatment of choice. Patients have shown improvement when progesterone has been administered in 5 mg. doses hypodermically twice a week for the last two weeks of one or two consecutive cycles, with an effective total dose ranging between 20 to 40 mg.

Endocrine therapy has yielded remarkable results in many cases, two or more years having elapsed after its use without recurrence of symptoms. It is strongly recommended.

Other forms of treatment have varied from simple reassurance to the performance of mastectomy.

Adenosis.—Adenosis (Schimmelbusch's disease) is most frequently observed in women between the ages of 35 and 44 years. It is characterized by the occurrence in one or both breasts of multiple nodules which measure from 1 mm. to 1 cm. in diameter and are usually distributed about the upper and outer hemisphere. In one third of the patients pain is a conspicuous feature. The breasts, as in mastodynia, are thickened, granular and tender, with the additional occurrence of multiple nodules. An edge can be palpated at the periphery of the diseased portion. This "caking" or induration may at times suggest cancer.

Adenosis is often superimposed on a persisting mastodynia and is much more chronic and more intractable to treatment.

The differential diagnosis from benign intracystic papilloma or from mammary cancer may require a biopsy.

The pathologic process may be limited or diffuse throughout the breast or breasts (figs. 2 and 3). Increased fibrous tissue through the parenchyma riddled with small cysts, minute adenomas, papillomas and dilated ducts is characteristic. There is much increase in the periductal and perilobular stroma. The intraductal hyperplasia and the epithelial proliferation of acini resemble those in various forms of cancer.

There is a definite relation between adenosis, mastodynia and cystic disease of the breast. Tissue excised from a patient with adenosis may show cysts, and that excised from a patient with cystic disease may show small areas of adenosis.

The patients fall into two endocrine groups: (*a*) Patients in early sexular maturity with small breasts due to stunting from high estrogenic

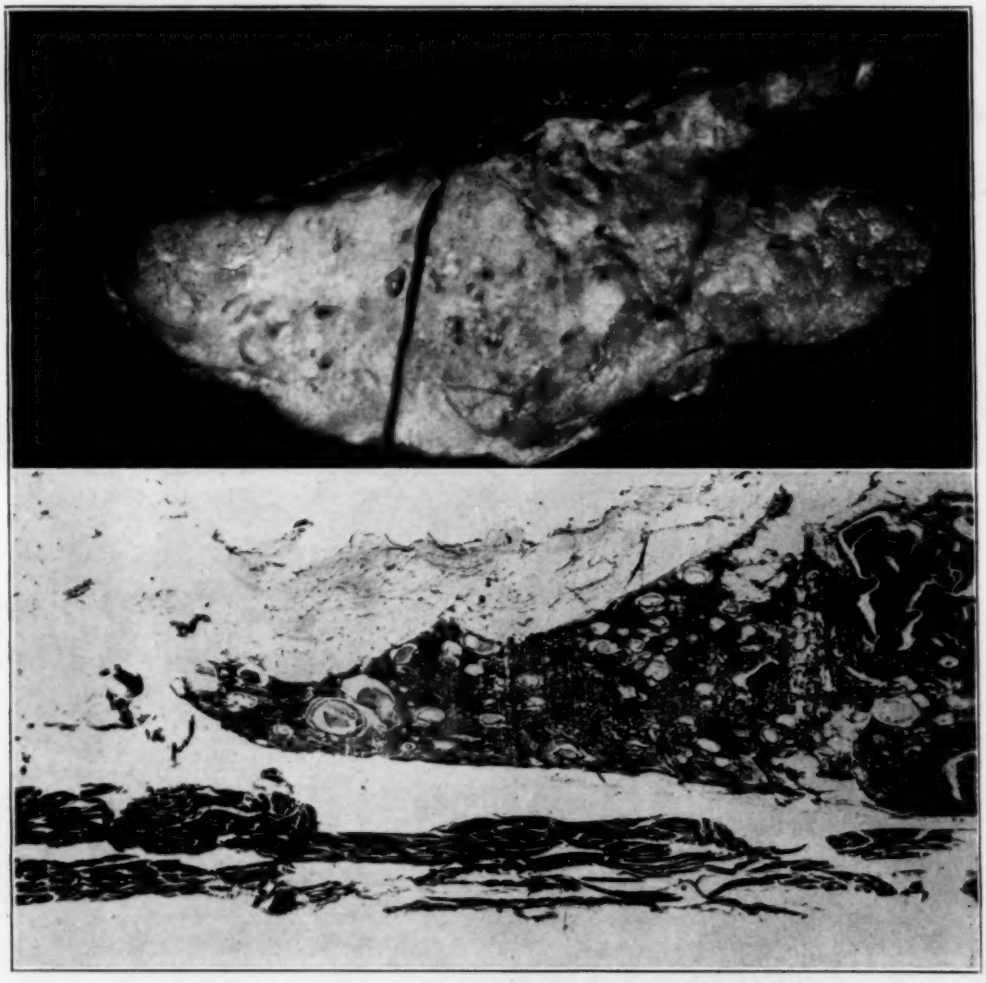

Fig. 2.—Specimen cross section and photomicrograph in a typical case of adenosis. The mammary tissue is fibrous, firm, contains small cysts in the periphery.

stimulation in adolescence. They may be in a relatively far advanced stage of the disease in their early twenties and may have an increased susceptibility to cancer. (*b*) Patients of 30 years of age or more, who have characteristic changes in the breast of one year's duration or more with pain and menstrual complaints and who are usually psychically

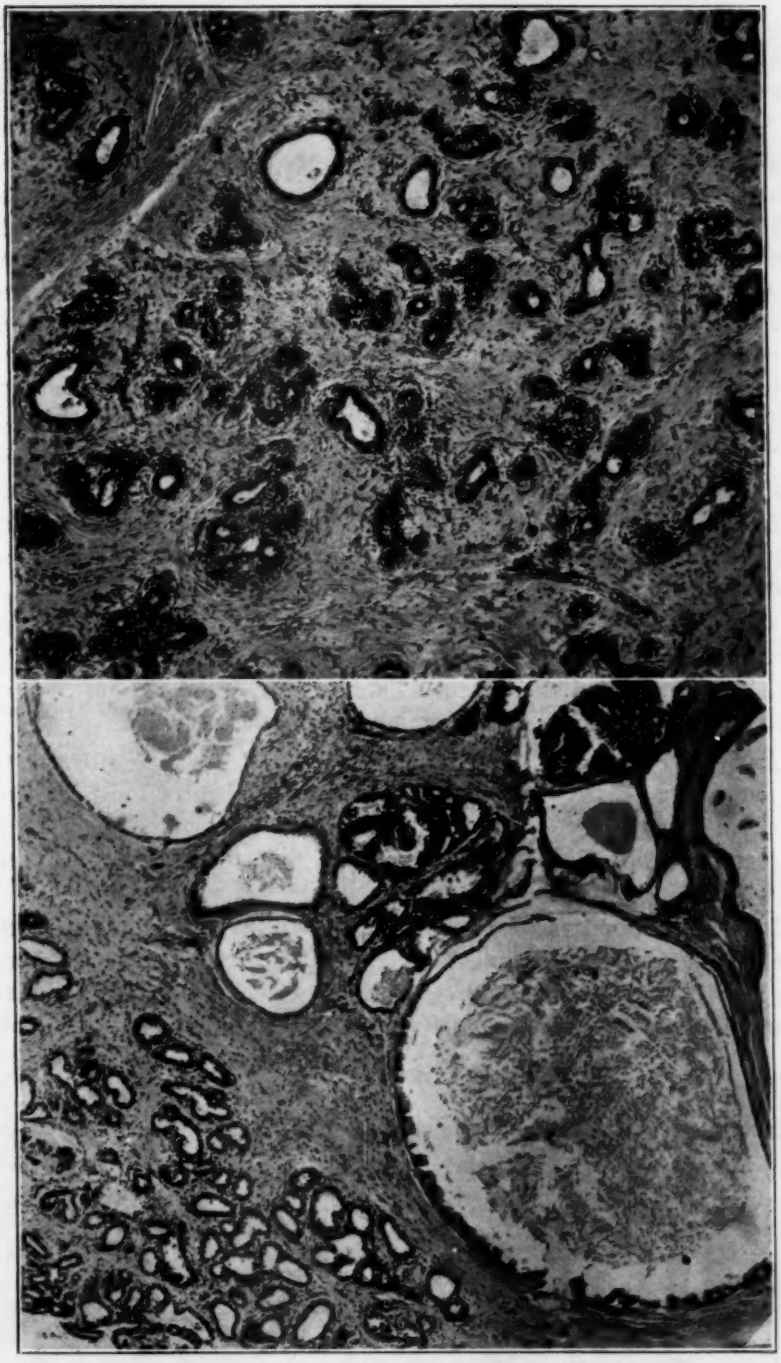

Fig. 3.—Photomicrographs showing intracystic papillomas and diffuse proliferation of lobule epithelium in adenosis of the breast.

upset. These symptoms are common in both groups, but in this group they seem to be due to a prolonged moderate hyperestrinism brought about by low function of the corpus luteum over a period of years. The secretion of estrogen is usually found to be within normal limits.

While the changes seen in mammary dysplasia are not essential to the development of mammary cancer, they do represent changes due to hyperestrinism which, as observed in a definite percentage of animals, ultimately lead to the development of cancer in the breasts. Clinically, Geschickter [5a] found that among patients with adenosis of the breast who were carefully followed the incidence of cancer was 2 per cent while among those with cystic disease the incidence was 0.79 per cent. The incidence of cancer of the breast is definitely higher among women with chronic mastitis than among women as a whole, for whom the incidence is 0.42 per cent.[6]

Treatment: Therapy in adenosis must be based on an accurate appraisal of the condition. Investigation of all doubtful cases is necessary. Nodules which are distinct and larger than usual or growing noticeably larger must be excised and sectioned, whether the nodule is cystic or solid.

Amputation of the breast to prevent possible development of cancer is not justified. On the other hand, biopsies which are difficult of pathologic interpretation or which show early cancer leave no recourse to the physician except that of doing radical mastectomy.

Estrogenic therapy is not satisfactory in adenosis. Patients with this condition already have a relative hyperestrinism of long standing, which in animal experiments leads to the development of cancer. It is, therefore, not considered coincidental that there is an increased incidence of cancer among patients with adenosis of the breast.

Progesterone therapy has given symptomatic relief in most of the patients treated, but the small discrete nodules, which are usually cysts, may persist. Aspiration of these cysts may be indicated to obliterate them. Progesterone is administered in 5 mg. doses hypodermically twice a week, from 20 to 60 mg. being given as a total dose between two or three menstrual cycles.

Recurrence may be encountered after two or more years.

Cystic Disease.—Women at or near the menopause form the largest group of patients with cystic disease of the breast. The greatest incidence is found in women between the ages of 41 and 45 years. The

6. Warren, S.: The Relation of Chronic Cystic Mastitis to Carcinoma of the Breast, Surg., Gynec. & Obst. **71**:257, 1940. Lewis, D., and Geschickter, C. F.: The Relation of Chronic Cystic Mastitis to Carcinoma of the Breast, ibid. **66**: 330, 1938.

disease predominates in childless women in the ratio of 3 to 2. For women with children at least from four years to a decade has elapsed between the time of the last pregnancy and the onset of the disease.

Few patients with cystic disease have menstrual disorders or difficulties with childbearing. The menstrual disorders encountered are associated with the menopause. Therefore, the fact that a large number of childless women and a large number of women approaching the menopause are affected is a striking etiologic factor from a clinical standpoint.

When assays of the urine for estrogen and pregnandiol were carried out and linked with experiments on controlled rats receiving large injections of estrogen and small injections of progesterone, Geschickter and others [7] found evidence to support the probability that an intense or unopposed estrogenic stimulus results in the formation of cysts. The period of stimulation may be brief, and the withdrawal of the stimulus, followed by secretory activity, may play a role in the development of the large cysts.

The symptoms of cystic disease usually appear abruptly or are of a relatively short duration, the period being in terms of days or weeks. The chief complaint is the discovery of a lump. A minority of patients notice mild pain, soreness and a burning or sticking sensation prior to the appearance of the cystic lump.

The breasts affected are usually fairly large or adipose. The cysts are usually found away from the periphery of the breast. The tumor is round, smooth, tense and freely movable. Fluctuation can be made out in some cases. Cysts may change in size and tend to disappear in about 7 per cent of the cases. The upper hemisphere is more frequently affected.

In a large number of cases only one cyst of appreciable size is found, but single cysts may be found in both breasts in 11 per cent of the patients.

Multiple cysts are found in one or both breasts in 25 per cent of cases at the first examination. They occur in a slightly younger age group, and the symptoms are similar to those associated with adenosis. This tendency to multiplicity and bilateral involvement certainly suggests an underlying endocrine disturbance, whcih is further substantiated by endocrine studies of the urine excreted by the patients.

The tumor and the breast can be transilluminated well. The majority of the cysts project into the fat over the breast and are easily aspirated, yielding a cloudy or a serous fluid. A thick, fibrous, walled cyst deep in the breast makes diagnosis difficult, and if aspiration is unsuccessful, exploration should be resorted to.

7. Geschickter.[5a] Astwood and Geschickter.[5b] Bonser.[5c] Gardner.[5d]

Treatment: The treatment of choice is excision of the cysts (84 per cent of the patients are free from further complaints). In 15 per cent of the patients other cysts develop in the breast. Recurrent tumors of the breast in patients past the menopause must be held to be suggestive of cancer until accurately diagnosed.

At operation the mammary cyst appears as a tense, bluish, walled cyst embedded in dense, fibrous stoma. Multiple small cysts and dilated ducts may be seen in the surrounding tissue. Lobule structure is poor. Microscopically the lining epithelium of the cyst is often replaced by fibrous tissue, or the persistent cuboidal epithelium contains

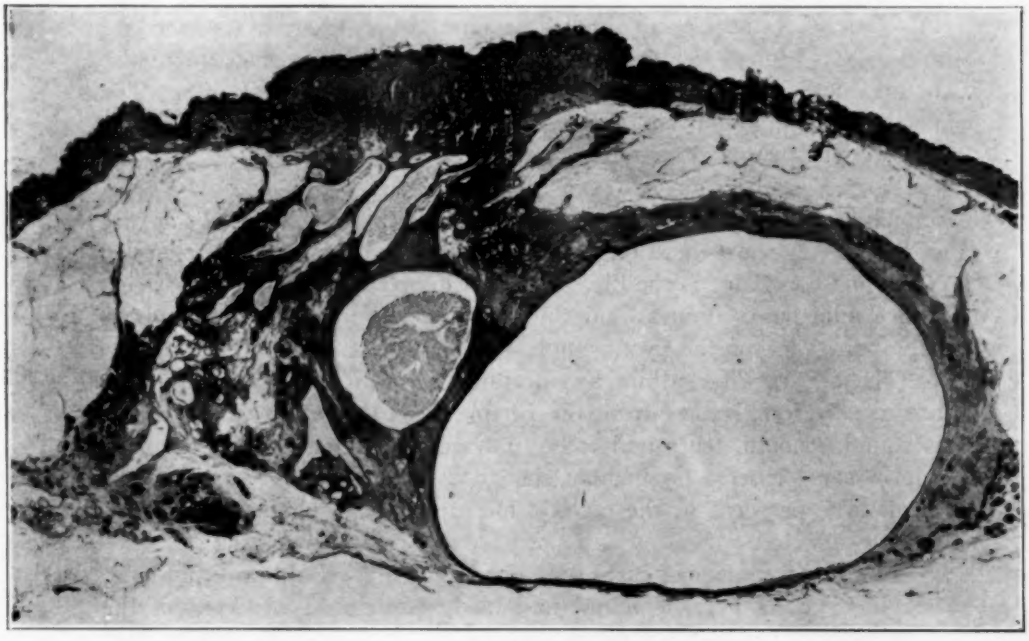

Fig. 4.—Cystic disease. Cysts centrally located as noted in macroscopic cross section.

eosin-staining cytoplasm. The surrounding ducts and lobules show involutional changes. The lobules are small and undergo dilation or regression. The adjoining tubules are dilated and may contain secretion. There is a decided increase in fibrous stroma (figs. 4 and 5).

Cancer cysts and intracystic papillomas are not the result of this process. They more often affect the large ducts near the nipple after the menopause. Cancer, however, is found in 0.74 per cent of patients with cystic disease. Simple cysts herein described affect the smaller ducts and terminal tubules and occur prior to or during the menopause.

Progesterone has apparently been of some value in prevention of the recurrence of cysts in patients with a tendency toward recurrence

after surgical intervention. Endocrine therapy should be instituted only when accurate information exists.

B. BENIGN NEOPLASIA

Fibroadenoma.—Fibroadenoma is the most common benign tumor of the breast in young women in the childbearing age. Its firm and

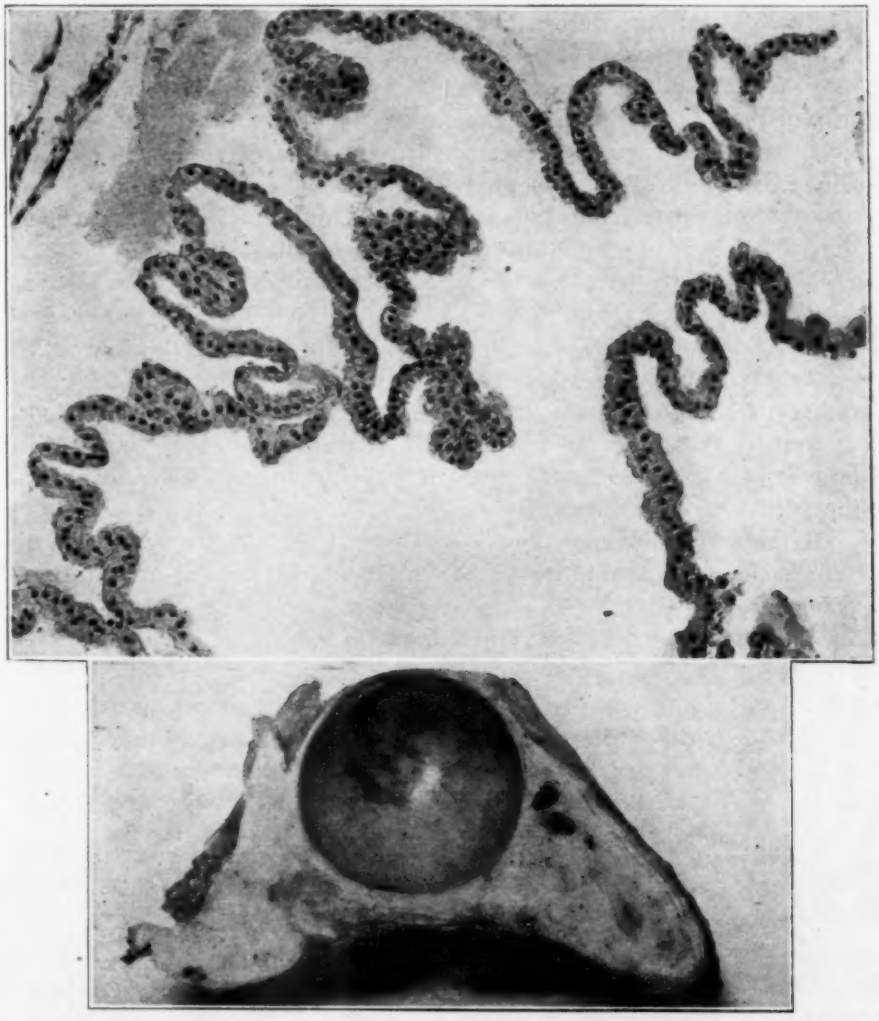

Fig. 5.—Cystic disease. Gross and microscopic cross sections of the cyst wall.

encapsulated character [8] together with its mobility makes the diagnosis relatively easy. The average age at which it occurs is around 22 years.

8. Bloodgood, J. C.: Benign Tumors of the Breast: Encapsulated Adenoma, Ann. Surg. **79**:172, 1924.

Gradual enlargement of a single tumor over a period of months or years is the rule. In early adolescence, during pregnancy or toward the menopause more rapid growth has been noted to appear. These are the times when high concentrations of estrogen are found. The tumor also responds to menstruation.

The breast containing the fibroadenoma is usually well developed. While a solitary lesion is usually found, multiple growths may be present. The tumor must be differentiated from cancer, cystic disease or some other rare, firm lesion of the breast. The lack of retraction of the nipple or of atrophy of the skin together with the average age incidence are helpful points in diagnosis. The tumors are composed of a growth of ducts and an abundance of periductal connection tissue (fig. 6). The connective tissue is dense in slow-growing tumors but takes on a loose myxomatous character in tumors of rapid growth. The latter group is designated by many authorities as intracanalicular myxoma.[9]

Fibroadenoma has been experimentally produced by Geschickter, Lewis and Hartman [10] in the rat and monkey by stimulating the breasts with high, intensive doses of estrogenic substance. A constant level of the hormone is necessary as fluctuation does tend to produce cysts rather than fibroadenomas. This is in keeping with the observations in women, in whom the growth of fibroadenomas occurs during the periods of adolescence, early pregnancy and the menopause rather than the period of cyclic menstruation.

Treatment: Excision should be done at once in the treatment of these tumors, since this makes the diagnosis certain and avoids large tumor growths and the occasional complicating factor of sarcoma or carcinoma. After excision, fibroadenoma may reappear in about 10 per cent of the cases either in the same breast or in the opposite one.

Toward the menopause, giant myxoma or fibrosarcoma may develop in fibroadenoma, slowly growing over a period of five or six years with rapid enlargement toward the end.[11] The tumors are large, with great cystic spaces into which fibrous polypoid masses project. These

9. Oliver, R. L., and Major, R. C.: Cyclomastopathy; A Physiopathological Conception of Some Benign Breast Tumors, with an Analysis of Four Hundred Cases, Am. J. Cancer **21**:1; 1934.

10. Geschickter, C. F.; Lewis, D. D., and Hartman, C. G.: Tumors of the Breast Related to the Oestrin Hormone, Am. J. Cancer **21**:828, 1934.

11. Emge, L. A., and Murphy, K. M.: The Influence of Long Continued Injections of Oestrogen on Mammary Tissue, Am. J. Obst. & Gynec. **36**:750, 1938. Owens, F. M., and Adams, W. E.: Giant Intracanalicular Fibroadenoma of the Breast, Arch. Surg. **43**:588 (Oct.) 1941. Cooper, W. G., Jr., and Ackerman, L. V.: Cystosarcoma Phyloides, Surg., Gynec. & Obst. **77**:279, 1943. Geschickter, C. F.: Giant Mammary Myxoma, in Diseases of the Breast, Philadelphia, J. B. Lippincott Company, 1945, p. 319. Oliver and Major.[9]

masses are made up of myxomatous connective tissue in polypoid fibrous structures covered by cuboidal epithelium as seen under the microscope. There is a definite incidence of sarcoma in this group. The differentiation between giant myxoma and fibrosarcoma is not easy and requires careful microscopic study and experience in some cases. If sarcomatous

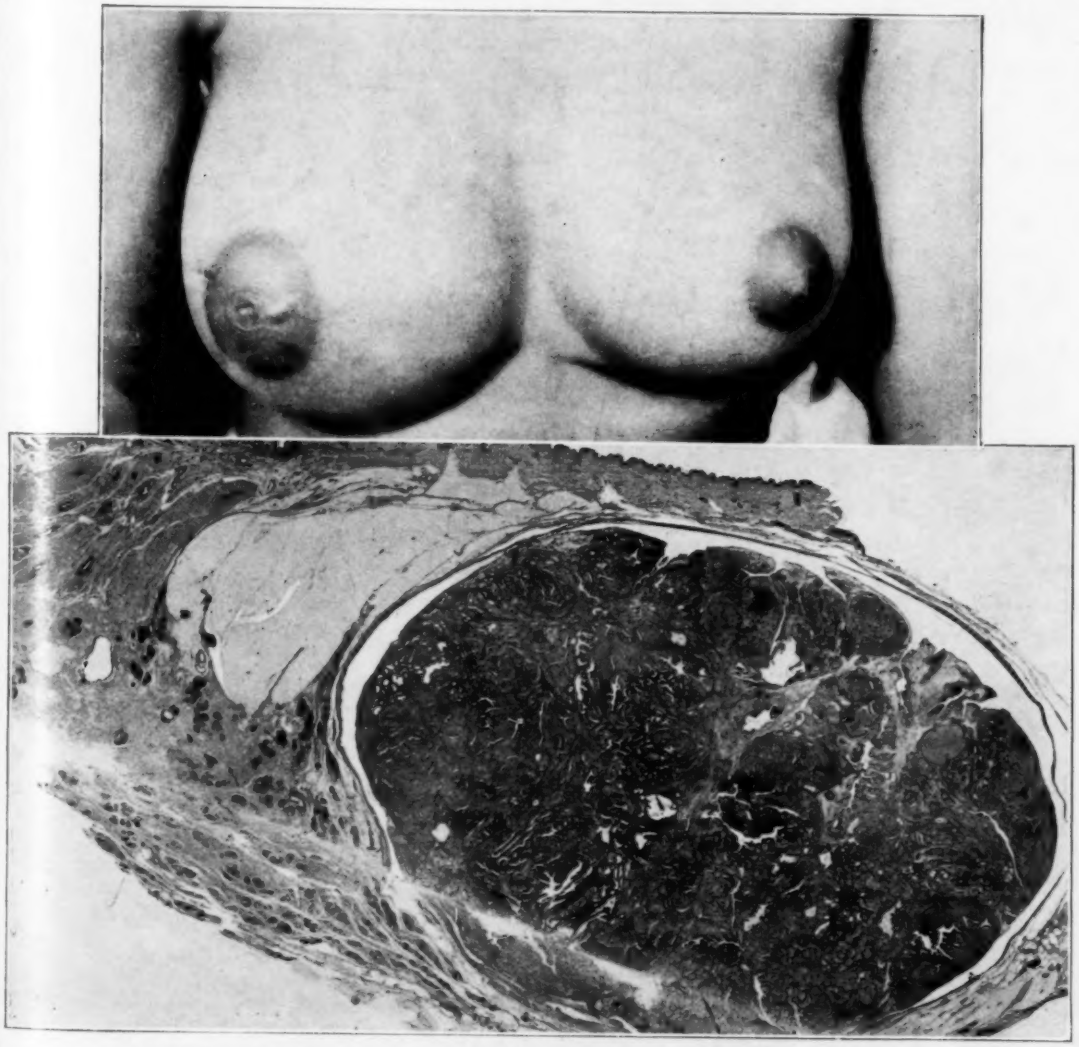

Fig. 6.—Photograph of a benign fibroadenoma and cross section of the breast.

change is found, amputation of the breast including the pectoral fascia, without axillary dissection, is indicated. The lesions do not as a rule metastasize to regional lymph nodes. Wide local excision is indicated for the benign lesions.

Benign Intracystic Papilloma.—Benign intracystic papilloma includes (1) papillary invaginations of the larger ducts, (2) intracystic papillomas and (3) papillary hyperplasia which occurs in adenosis of the breast. The condition, with the exception of papillary changes seen

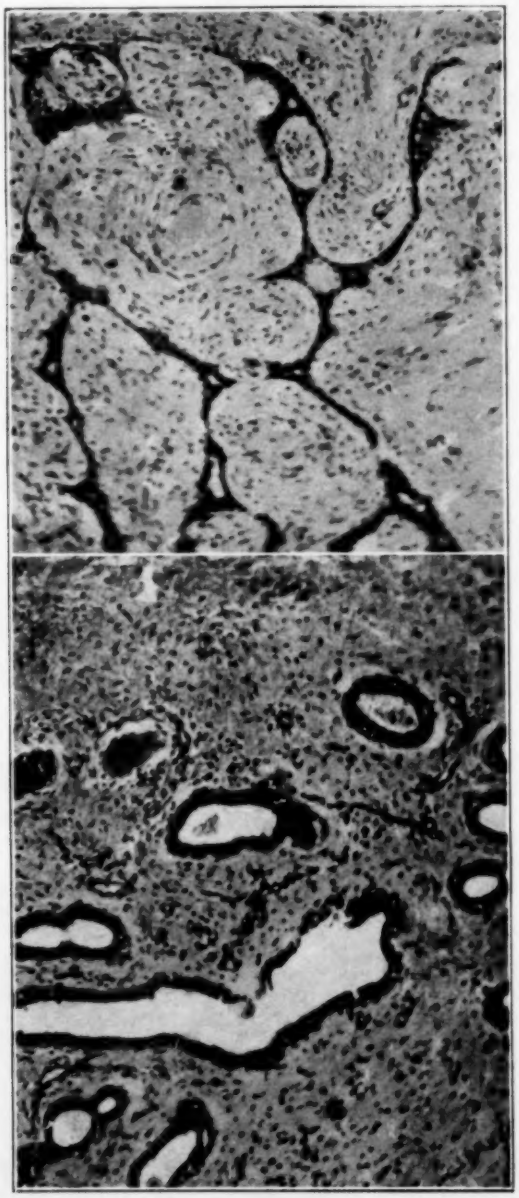

Fig. 7.—Intracanalicular myxoma. Photomicrographs showing periductal proliferation of fibrous stroma and polypoid, myxomatous fibrous structures covered with cuboidal epithelium.

in patients with adenosis of the breast, occurs usually in women near, at or beyond the menopause. It occurs with equal frequency in nulliparous and in parous women.

The tumors vary from 1 to several centimeters in size. They occur in the central zone of the breast and are frequently associated with a sanguineous discharge from the nipple. Evidence of a lump may have existed for from six months to five years. The mass is soft, compressible and usually freely movable, is shown on transillumination to be an opaque area and causes bloody discharge from the nipple when compressed. The tumor has at times been referred to as a low grade papillary or duct cancer.

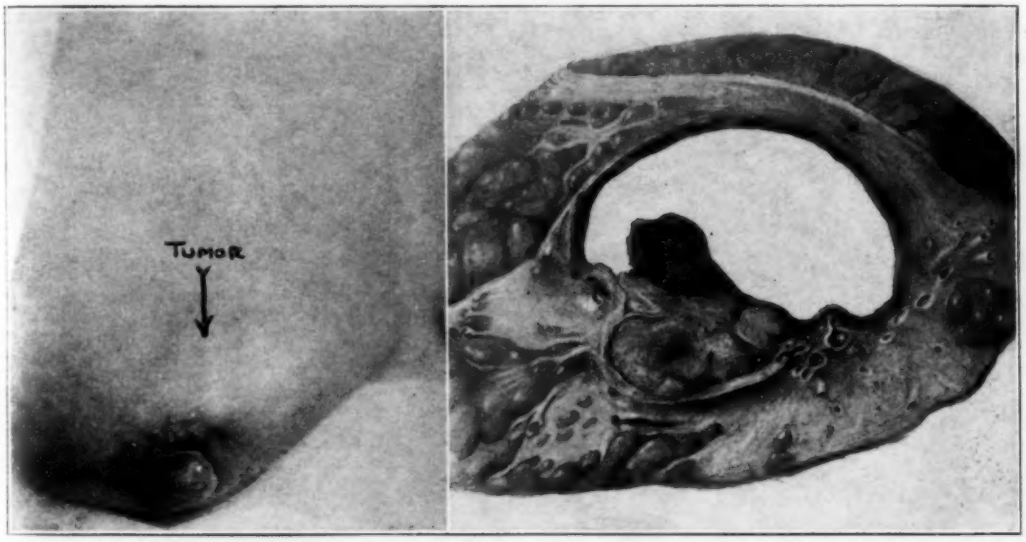

Fig. 8.—Benign intracystic papilloma. Clinical appearance of breast and cross section of a specimen.

The tumors are best treated by excision. They should be excised along with a zone of surrounding breast tissue. The wall of the cyst at the base of the papilloma must be examined under the microscope. If infiltration of the process occurs into or beyond the cyst wall or if malignant changes are noted in the papilloma, radical mastectomy should be performed.

The benign tumors on excision are found to be encapsulated (figs. 8 and 9). The papillary lesion may completely fill the cyst cavity. The cavity may be multilocular and filled with small papillomas. The papilloma is composed of branching tuftlike stalks festooned with

epithelial covering. The central stalk carries the blood supply and is the only attachment of the papilloma to the cyst wall. The epithelium over the fibrous core is in orderly arrangement and usually two layers thick. The outer layer is composed of tall columnar cells.

Tumors over 5 cm. in diameter frequently show malignant changes.

Fig. 9.—Benign intracystic papilloma. Photomicrograph showing stalk of papilloma.

In adenosis of the breast, papillary hyperplasia is common in women between the ages of 30 and the early forties. Both breasts are usually affected, and the lesions are toward the periphery.

The breasts are usually small and unequal in size. Multiple pea-sized nodules are felt in one or both breasts. Bloody discharge from the nipple may occur in 4 per cent of the cases.

The tumors are usually noted to fluctuate frequently in size at first. Pain accompanies the formation of tumor in about half the cases.

Because of the fact that papillary hyperplasia is widely distributed in the breast or breasts in adenosis, the site of the exploratory incision is chosen with great difficulty. This is especially true in the presence of blood from the nipple. The duct or area can usually be located by transillumination or palpation to observe the place from which the blood can be expressed. The questionable areas must be explored and the affected zone excised. The tissue must be examined histologically, as cancer may be a definite possibility. Microscopically the lobule buds of the terminal tubules show cystadenomatous change, namely, epithelial proliferation in dilated terminal tubules. Some of the cystic tubules seem completely filled.

Adair [12] stated that bleeding of the nipple occurs about as often in benign conditions of the breast (57 cases) as in malignant conditions (51 cases).

Geschickter,[13] in studying the over-all picture of the bleeding nipple, found that it occurred in only 4 per cent of all instances of cancer of the female breast. This symptom preceded the appearance of a breast tumor in only 22 of 100 instances of benign lesions studied. He concluded, however, that any bleeding from the nipple must be carefully studied and the cause eradicated because potentially benign papillomas may become malignant.

An intriguing endocrine origin for intracystic papillomas has been suggested by Geschickter,[13] based on these three factors: (1) the presence of epithelial buds which are remnants of normal mammary development; (2) their distribution along the large ducts or at the terminal tubules, and (3) prolonged regenerative activity in the buds. Usually the last factor occurs at the menopause or after prolonged estrogen stimulation. This estrogenic stimulation must be constant and prolonged but not necessarily of high intensity. In experiments on female rats, begun at birth, the mammary gland was constantly stimulated with estrone pellets after seventy days of injections of 25 gamma of estrone in oil twice daily. The author found that fibroadenomas occurred in one hundred and thirty to one hundred and ninety days but that papillomas appeared only after three hundred and fifty to five hundred and fifteen days.

12. Adair, F. E.: Sanguineous Discharge from the Nipple and Its Significance in Relation to Cancer of the Breast, Ann. Surg. **91**:197, 1930.

13. Geschickter, C. F.: Bleeding from the Nipple and Benign Intracystic Papilloma, in Diseases of the Breast, Philadelphia, W. B. Saunders Company, 1945, p. 325.

Endocrine therapy for this group of tumors does not seem warranted and indeed may be hazardous in view of the endocrine factors involved in the formation of the lesions, which may be followed even by the production of cancer.

SUMMARY

Mammary dysplasia and benign neoplasia have been presented with reference to the clinical aspects of the diseases involved.

The endocrine aspects of the various entities have been emphasized.

Treatment has been discussed including endocrine therapy.

It is hoped that this presentation will stimulate further consideration of the cause and treatment of this group of diseases of the breast.

SURVEY OF INTESTINAL OBSTRUCTION

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BEVERLY HILLS, CALIF.

THE INTRODUCTION of the use of indwelling gastric and intestinal siphonage by Wangensteen [1] and the use of intravenously administered fluids and plasma and blood replacement as well as of other therapeutic and diagnostic aids, particularly the antibiotics and roentgen examinations, have allayed some of the dread of acute intestinal obstruction.

Many physicians are now reasonably sure of themselves as regards the differential diagnosis between strangulating and simple obstructions and the technical management of affected patients. The mortality, however, remains much too high.

An attempt has been made to survey the management in the last five years of acute intestinal obstruction occurring at the Los Angeles General Hospital. It was not the purpose of the study to go into detailed clinical and laboratory findings but rather to search for possible pitfalls of omission or commission as well as for surgical blunders and, in reflection, to see if one might not do differently if again faced with a similar situation and thereby possibly save lives.

The survey shows a mortality rate comparable with that found in similar institutions handling a large number of acute surgical emergencies in spite of the fact that in Southern California there is the additional problem of the presence of aged people who have been inherited from other states and who, aside from intestinal obstruction, are in poor physical condition. In 1940 McKittrick and Sarris,[2] of the Massachusetts General Hospital, reported a mortality of 18 per cent among 124 patients operated on. In July 1946 Calihan and his associates,[3] of the Johns Hopkins Hospital, presented a ten year survey of 204 cases of surgical obstruction including cases of simple obstruction, volvulus, internal hernia and intussusception; a mortality of 20 per cent was

Read at the Fifty-Fourth Annual Meeting of the Western Surgical Association, Memphis, Tenn., Dec. 6, 1946.

1. Wangensteen, O. H.: Intestinal Obstruction, Springfield, Ill., Charles C Thomas, Publisher, 1945, pp. 6-7.

2. McKittrick, L. S., and Sarris, S. P.: Acute Mechanical Obstruction of the Small Bowel: Its Diagnosis and Treatment, New England J. Med. **222**:611-622 (April 11) 1940.

3. Calihan, R. J.; Kennedy, J. D., and Blain, A., III: Intestinal Obstruction: Study of Two Hundred and Four Acute Cases with Reference to Possible Efficiency of Antibacterial Therapy, Bull. Johns Hopkins Hosp. **79**:21-33 (July) 1946.

reported. In an identical group of 309 surgically treated patients the mortality was 21 per cent. In 1945 Griffin, Bartron, and Meyer,[4] of the Cook County Hospital, reported a mortality of 40 per cent in volvulus of the sigmoid associated with operative and nonoperative procedures. A similar mortality was reported by Dennis,[5] of the University of Minnesota Hospital. In our own series of volvulus of the sigmoid the mortality is 37.5 per cent.

During five years, 1941 to 1945 inclusive, 11,590 major operations were done in general surgical cases at the Los Angeles General Hospital. This is exclusive of operations in the other surgical specialties such as orthopedic, neurosurgical or gynecologic operations. During this time, surgical treatment was carried out in 1,107 proved cases of acute intestinal obstruction. Cases of ileus, peritonitis and possible or partial obstruction are not included in this group.

CLASSIFICATION

The classification of the different types of acute intestinal obstruction encountered is shown in table 1.

TABLE 1.—*Incidence of Acute Intestinal Obstruction at the Los Angeles General Hospital, 1941 to 1945*

Obstruction by bands and adhesions		359
Early postoperative	31	
Late postoperative	274	
Without previous surgical treatment	54	
Strangulated external hernia		292
Volvulus		72
Large bowel	27	
Small bowel	45	
Carcinoma of colon		105
Sigmoid and descending colon	90	
Splenic flexure	9	
Transverse	6	
Hepatic flexure	9	
Cecum and ascending colon	11	
Carcinoma of rectum		27
Diverticulitis		24
Intussusception		39
Strangulated internal hernia		11
Mesenteric thrombosis		38
Congenital anomalies		32
Imperforate anus	13	
Congenital atresia	7	
Megacolon	4	
Meckel's diverticulum	8	
Gallstone or foreign body		7
Endometriosis		2
Regional ileitis		4
Extrinsic tumor		5
Primary tumor of the small bowel		3
Metastases, terminal		51
Obstruction from superior mesenteric artery		2
Tuberculosis of the cecum and peritoneum		5
Radiation obstruction		1
Stricture of the rectum		5
Trauma		3
Total		1,107

4. Griffin, W. D.; Bartron, G. R., and Meyer, K. A.: Volvulus of the Sigmoid Colon: Report of Twenty-Five Cases, Surg., Gynec. & Obst. **81**:287-294 (Sept.) 1945.

5. Dennis, C.: Treatment of Large Bowel Obstruction: Transverse Colostomy; Incidence of Incompetency of Ileocaecal Valve; Experience at University of Minnesota Hospitals, Surgery **15**:713-734 (May) 1944.

Because of limitation of time and space, the paper will be limited to that part of the survey covering bands and adhesions, volvulus and strangulated external hernia.

BANDS AND ADHESIONS

Cases of obstruction by bands and adhesions were grouped according to whether the obstruction was early postoperative or late postoperative, the former occurring during the first month after abdominal operation.

Early Postoperative Obstruction.—There were 31 patients for whom the diagnosis of early postoperative obstruction was made. There were, no doubt, more similarly affected, but because of the policy of the hospital of intubating immediately in all suspected cases as well as in all cases of acute abdominal conditions requiring surgical treatment, the

TABLE 2.—*Surgical Procedures in Late Postoperative Obstruction by Bands and Adhesions at the Los Angeles General Hospital, 1941 to 1945*

Number in whom surgical procedures were carried out for late postoperative obstruction by bands and adhesions	328
Total number treated surgically	189
Adhesions released (mortality, 5.4%)	146
Resections (mortality, 28.7%)	24
Enterostomy	5
Perforation closed	4
Enteroenterostomy	4
Cecostomy	3
Invagination of the necrotic area	1
Closure of the fecal fistula	1
Plication to prevent recurrence (mortality, 36.8%)	1
Average surgical mortality	11.1%

number has been held rather low. Ten patients were reoperated on, 3 of whom died.

Possibly in at least 1 case it was inadvisable to reoperate, as in the search for adhesions an abscess was encountered, with resultant soiling and fatal peritonitis. Inflammatory reaction in the vicinity had accounted for the obstruction. That few such cases are found in this category is ample proof that our surgical staff is mindful of the fact that obstruction due to inflammatory processes will as a general rule respond to suction siphonage.

Late Postoperative Obstruction.—Cases of late postoperative obstruction by bands and adhesions constitute a large proportion of the total cases of intestinal obstructions. In this survey it was found in 328 patients; 274 of these had previous surgical treatment, and for 54 either it was specifically stated that there had been no previous operation or nothing could be found in the history or physical examination which indicated a previous operation.

Obstruction by adhesive bands is indeed no respector of age. The youngest patient was 4 days old and the oldest 86 years. Thirty patients were above 70 years of age, and 72 were above 60. There were 139 treated by suction only, and 189 were operated on. Table 2 shows the operative procedures and the mortality.

Simple Versus Strangulating Obstruction.—As I studied the histories, I was soon convinced of two facts: 1. The duration of the obstruction had nothing whatsoever to do with the degree of obstruction present. A twelve hour obstruction was often gangrenous while a three day obstruction might be perfectly harmless. 2. The differential diagnosis between an early strangulating lesion and a simple obstruction, made on the presence or absence of tenderness as described by Wangensteen, was not so easily established.

McKittrich and Sarris stated in their report that they were unable to make this early differential diagnosis. Calihan and others, in their survey of July 1946, stated:

> In the papers by some of the proponents of conservative therapy who claim to be able to differentiate strangulation there can be found incidents where strangulation had been temporized with disastrous results. The burden of responsibility therefore rests on the surgeon who attempts to make this early differentiation and finds after an interval of conservative therapy that his patient has a strangulated obstruction.

Among the patients covered by this survey 8 deaths in the group with obstruction by bands and adhesions could possibly be attributed to delay and failure in recognizing the strangulating lesion. The 8 patients who died were treated with siphonage for from two to seven days before surgical intervention. Four additional patients who lived might possibly have been spared a resection had surgical intervention not been delayed because of the calming influence of the Miller-Abbott tube.

Strangulation occurred in 32 per cent of McKittrick's 136 cases, and in Dixon's group of 166 patients at the Mayo Clinic 26 per cent were strangulated.[6] This is a high percentage, and one might well ponder before glibly slipping in a nasal tube with the idea that that will take care of things for the next twenty-four hours.

Pitfalls in Management.—In looking for pitfalls in management, it was not felt that preoperative suction and fluid replacement, which were carried out in all patients without exception, could be criticized. Blood or plasma, or both, was given in about 60 per cent before or during the surgical procedure. I consider this to be an average percentage, but it

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6. Schlicke, C. P.; Bargen, J. A., and Dixon, C. F.: Management of Intestinal Obstruction: Evaluation of Conservative Therapy, J. A. M. A. **115**:1411-1416 (Oct 26) 1940.

should be given in all, since Coller [7] has shown that the loss of blood and plasma is usually greater than it appears to be on the surface. For 2 patients who went into shock on the operating table no record was found of blood or plasma having been given.

In looking for technical errors, I found the following: The youngest patient, 4 days old, was examined, and a diagnosis was made of intestinal obstruction due to the presence of meconium. The abdomen was apparently thoroughly explored, but at autopsy a single violin band of adhesions was found completely obstructing the upper part of the ileum.

There was 1 case in which a cecostomy was performed for obstruction of the small bowel. This is a surgical blunder, and one might wonder what went through the surgeon's mind. It happened in this manner: There was great distention, and a flat plate roentgenogram of the abdomen revealed what the surgeon interpreted as a dilated large bowel. The cecostomy was done in the belief that there was an obstruction at the sigmoid.

This brings up the matter of the interpretation of the flat plate roentgenogram. It is not always easy to differentiate between the small and the large bowel under considerable tension. Many of these emergencies happen at night. It would be a great help if a roentgenologist were on call to interpret properly and to report on a roentgenogram after a barium enema when indicated. So far, however, I do not know of a single hospital in which the department of roentgenology is anxious to share this idea with the surgeon.

In 1 patient a loop of intestine was caught between the lateral wall and a colostomy opening performed at the sigmoid elsewhere. This could have been avoided if the surgeon had closed the gutter when performing the colostomy.

There were three possibly avoidable technical errors in which perforation and soiling occurred during the exploration of distended loops of intestine to find the obstruction. Aspiration to deflate by one of the methods described by Wangensteen might have prevented this. To perform an aseptic anastomosis after such soiling as was done in the cases concerned is obviously incongruous.

This brings up the problem of aseptic anastomosis. In eight resections the surgeon definitely dictated an aseptic type and in ten an open type of anastomosis. Of the 10 patients in whom open resection was performed, only 1 died, while of the 8 in whom aseptic anastomosis was done, 3 died. In these 3 the perforations just mentioned occurred,

7. Coller, F. A., and Maddock, W. G.: Water and Electrolyte Balance, Surg., Gynec. & Obst. **70**:340-354 (Feb., no. 2A) 1940.

so no conclusions can be drawn from this. It is hoped that the discussions will bring out some sharp opinions on this matter. Wangensteen is of the opinion that aseptic anastomosis is of paramount importance, but we believe that this opinion is not universally shared.

The toxicity of the contents of the obstructed intestine is still debated. The value of penicillin has, however, been demonstrated by Blain and Kennedy, of the Johns Hopkins Hospital.[8] They were able to prolong the lives of dogs with strangulating obstruction and demonstrated that resection could be done in such dogs at a period which was twice the survival time of control dogs not treated with penicillin. It is hoped that the immediate administration of massive doses to all patients, entering the hospital with intestinal obstruction will materially lower the mortality rate, though penicillin should not be used as another adjuvant with which to temporize in the treatment of this disorder.

Patients who are repeatedly returning to the hospital with acute intestinal obstruction present a real problem. I know of 2 patients who have been admitted on occasions too numerous to mention. One of them, a nurse, had been admitted thirty times. Most patients are best treated by suction, but there again there is a pitfall. One patient was admitted five times and relieved by suction. On the sixth admission he was again treated with siphonage, but this time he had a strangulating lesion, which was not recognized early. Enterostomy was performed but he died.

In this survey I found that 81 patients had had previous surgical treatment for obstruction and 41 had had previous suction. About one half of these had both. It is with such patients that one should be doubly cautious. It is so easy to look up the past history and note that they were previously relieved by suction and then to resume siphonage only to find that because of temporization a strangulating lesion has developed.

The folly of meticulously separating massive adhesions is well known. The method of plicating intestine as described by Noble has been resorted to on a few occasions. I have formed no conclusions on this procedure and trust that some one will enlighten me. It appears that, if not too extensive, resection of the matted coils would still be preferable; the resection should be done at a quiescent stage between the flare-ups of acute intestinal obstruction.

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8. Blain, A., III, and Kennedy, J. D.: Effect of Penicillin on Experimental Intestinal Obstruction: Studies on Strangulated Low Ileal Obstruction, Bull. Johns Hopkins Hosp. **79**:1-20 (July) 1946.

The experimental use of intraperitoneally administered heparin has recently been tried by Lehman [9] in the hope of preventing adhesions. The contraindication for its use is a bleeding raw surface. Unfortunately, it is in the presence of this that one would consider it a godsend to have something which could prevent adhesions. The use of heparin therefore seems of doubtful value.

SUMMARY

A survey has been made of the occurrence in the last five years of acute intestinal obstruction at the Los Angeles General Hospital.

The mortality of this condition there as elsewhere remains too high.

Delay in recognizing a strangulating lesion and technical errors constitute the major factors in keeping the mortality rate high. Technical errors are too frequent. Delay is due in no small part to the calming influence of indwelling siphonage both on the patient and on the surgeon, who before the advent of suction had a more wholesome respect for acute intestinal obstruction than he has now.

It is worth repeating that the differentiation between a simple lesion and an early strangulating one is not necessarily easy. Operation may be avoided in a fair number of patients, but it is of greatest importance that it be withheld even temporarily only in cases in which there is no question whatsoever of strangulation of the bowel.

As the threshold of shock in a patient with acute intestinal obstruction is low, we believe that no patient should be allowed to have surgical treatment without having first received blood or plasma or both.

The recent experimental work at the Johns Hopkins Hospital in the early use of massive doses of penicillin is promising.

It is urged that the surgical sections and the departments of roentgenology of hospitals have a yearly intensive review of all types of intestinal obstruction. In this manner, certain pitfalls of diagnosis and management would be brought to light, and better operative results would be obtained.

DISCUSSION

Dr. Willis D. Gatch, Indianapolis: I am sorry that I have to discuss this important paper without having studied it before its presentation. I think, however, that I can discuss some points made in it with profit.

Obstruction of the bowel is the most important subject in any consideration of abdominal surgery. Dr. Baumgartner's statistics on the causes of such obstruction, if I interpret them correctly, show that about one half of the cases were due to a preceding laparotomy. These studies show that there must be something seriously wrong with abdominal surgery. Peritoneal adhesions are necessary and cannot be prevented. Without them abdominal surgery would be impossible. I,

9. Lehman, E. P., and Boys, F.: Clinical Use of Heparin in the Peritoneum for the Prevention of Adhesions: Report of Fourteen Cases, Arch. Surg. **43**:933-945 (Dec.) 1941.

therefore, never had much sympathy with research work designed to prevent them, but I believe that any experienced surgeon would say that by the exercise of care, which must include general handling of tissues, the prevention of drying of the peritoneal surfaces, the sparing use of gauze packs and the intelligent use of omentum, the formation of dangerous adhesions can be prevented in most cases.

Several important discoveries on obstruction deserve discussion. First of these is that distention of the intestines is due practically entirely to swallowed air and that distention can be entirely prevented by the use of the Levine tube and continuous gastric suction. Dr. Singleton keeps up gastric suction for some time after every laparotomy. I use it whenever signs of gastric distention begin to appear. The second is that no case of obstruction of the bowel is an emergency. I heard a discussion of such obstruction years ago in this society, in which member after member would get up and emphasize the emergency nature of every case of such obstruction. They subscribed to the dictum, "Never let the sun go down on a case of obstruction of the bowel." The death rate in those days was 60 to 70 per cent. I think we should now adopt the motto, "Let no case of obstruction of the bowel be considered so urgent as to justify the omission of proper diagnostic study and proper preparation before operation."

Our routine is to take a roentgenogram of the abdomen after administration of barium enema as soon as the patient enters the hospital. This will settle at once whether or not the obstruction is in the large bowel. In case of obstruction of the small bowel, it will also give a good idea as to the site and seriousness of the obstruction.

I differ mildly from Dr. Baumgartner in regard to the diagnosis and proper handling of obstruction complicated by gangrene of the bowel. I agree with him that it is almost impossible to make this diagnosis in many cases. I have many times discovered at operation a loop of gangrenous bowel walled off and apparently doing the patient little harm. Under these conditions, I have found that simple excision of the gangrenous loop with gun barrel enterostomy will save nearly all these patients. We have had, in fact, about 10 consecutive cases without death. The bowel has tremendous powers of protecting itself against gangrene. We have shown that the bowel can endure six hours of total anemia without the patient dying. It is my belief that even when gangrene is suspected it is better to decompress the bowel and get the patient in good condition than it is to operate on him at once. It is extremely dangerous to operate on a dehydrated and starving patient with greatly distended loops of small intestine. In short, I am no longer as terrified by the appearance of a gangrenuos loop of bowel as I used to be.

The death rate from the treatment of femoral hernia complicated by gangrenous bowel has not improved in the last seventy years. We have recently treated 3 patients with this condition by a new method. The treatment consists, first, of simple drainage of the femoral sac, second, of decompression of the bowel down to its point of imprisonment in the femoral ring with the Miller-Abbott tube and third, of laparotomy through a low rectus incision, resection of the incarcerated bowel and lateral anastomosis between the ends of the intestine. Two of the patients were obese women between 65 and 70 years of age. The third was a woman of 80 years of age.

The Miller-Abbott tube has done a great deal to lower the death rate in bowel obstruction, but it is often misused. If you insert a Miller-Abbott tube, attach it to the suction apparatus and go away and leave it, you are doomed to disappointment. Once the tube is in the intestine, a nurse should be kept irrigating it con-

stantly and aspirating gas and fluid through it with a piston syringe. Under this management it is amazing how rapidly the tube will pass down the intestine.

DR. WILLARD BARTLETT JR., St. Louis: I had the privilege of reviewing this paper yesterday with Dr. Baumgartner and with Dr. Bern, the head of the Department of Surgery in the University of Southern California, on which service the patients reported on were largely treated.

I was struck very much, as they were, with one group of patients, on which Dr. Baumgartner did not have time to detail today, and I am going to call it to your attention because it is the group which challenges their interest most, as it does my own. I am sure few of you go along without seeing such patients in practice. A group of 27 obese patients with incarcerated umbilical hernias were operated on, with a mortality rate of 56 per cent. We have been mistaken with patients like this in the past, and I want to recount some bitter experiences of our own in the management of such patients and the principles we formulated for handling them, which have worked out to our satisfaction since.

Let me speak first of the obese patient with a large ventral hernia in which no incarceration occurs. Such a patient suffers from an increased intra-abdominal pressure. If one attempts to close that very large ring without first having reduced the weight of the patient to approximately the average weight to which his bony structure entitles him, one further increases the intra-abdominal pressure if there is success in getting the ring together. I think it is a fair statement that in 25 to 50 per cent of instances one cannot get the hernial ring closed at all at operation on a patient unprepared by the means I have described.

In patients, however, in whom one congratulates oneself on having got the ring closed under great tension, a characteristic train of symptoms develops immediately because of decrease in vital capacity. They become flushed, their pulse rate rises rapidly after they leave the table, their blood pressure goes up and breathing becomes stertorous. Pulmonary edema and atelectasis develop, and within the first twenty-four hours these patients will take one of two courses. They will get a deep breath in the course of their struggles for breath or during a coughing or vomiting episode and will get immediate relief. Their breathing will become comfortable, their pulse rate will slow down, their temperature will fall and their blood pressure will return to preoperative levels. That is a sign that the entire posterior suture line (at least) has pulled out. If they do not get that relief, however, they will die. The mortality is about 25 per cent, which is too great.

The person who not only is obese and has a large hernial defect but who also has intestinal obstruction has simply doubled the problem of increased abdominal tension due to intestinal distention, and the likelihood of fatal outcome is the more strongly present for such a person. It is not surprising, therefore, that the operative mortality is also doubled for such patients in the essayist's paper.

It has been our plan since the late twenties simply to cut the ring in such patients to allow two things: in the first place, one can see whether they have a gangrenous loop at the point of incarceration at the ring, and, in the second place, it permits ready movement back within the abdomen of some of the incarcerated loops, with the relief of incarceration.

The second important point of management at the operating table when one's hand is absolutely forced by the presence of incarcerated bowel which cannot be decompressed by suction is to do an enterostomy at a site remote from the incarceration—not a Witzel enterostomy but a "stab" enterostomy with a Pezzar catheter that does not involve wide opening of the peritoneum.

Thirdly, if the patient has a gangrenous loop (and only the minority of them will at the point of incarceration), that loop should be exteriorized.

DR. THOMAS G. ORR, Kansas City, Kan.: When some one discusses mortality rates in intestinal obstruction, I immediately want to know what he is talking about. One of the slides showed that 131 patients were treated without operation, with a mortality of 4.5 per cent. Were these really cases of intestinal obstruction? I believe that we should confine our definition of intestinal obstruction to those cases in which the bowel is actually mechanically occluded either with or without strangulation.

When the bowel is functionally obstructed, it of course can be treated without operation successfully in many cases. I believe that such cases should fall in another group and that we should keep the pathologic distinction clear when discussing mortality rates.

It is true that intestinal obstruction may be a difficult diagnosis to make. It may be difficult to distinguish from peritonitis and from paralytic ileus. It is certainly often difficult to differentiate between obstructions due to simple occlusion and those due to strangulation. Strangulated hernias were mentioned as a frequent cause of intestinal obstruction. Young physicians and surgeons should be taught to look for such a cause first when intestinal obstruction is suspected. I can now recall 2 patients who were treated by internists for several days before being sent to a hospital. Both of these patients died after late operations. In my experience internists more frequently miss the diagnosis of strangulated hernia than do surgeons.

DR. ARTHUR B. MCGRAW, Grosse Pointe, Mich.: I should like to ask Dr. Baumgartner to tell us the distribution of the different types of anesthesia in these operations which he has been reporting. I believe that it is fair to say that in operating for intestinal obstruction the factors which make the outcome of the operation unpredictable are the length of time the intestines are exposed and the amount of manipulation which is necessary in order to determine and deal with the site of obstruction. The kind of anesthesia used and the relaxation obtained thereby influence these factors of time and manipulative trauma and also influence the matter of whether there is inadvertent or necessary exteriorization of large amounts of the small bowel during operation.

During the past year, we have had at our hospital the services of a young and expert anesthesiologist, and he has gone far toward making us enthusiastic over the merits of gas anesthesia supplemented by curare in difficult abdominal surgery. In many cases of acute intestinal obstruction there are good reasons for not giving spinal anesthesia in spite of the relaxation obtained thereby.

I simply want to bear testimony to the help we have had with gas anesthesia and curare in handling some of our cases of intestinal obstruction.

DR. CONRAD J. BAUMGARTNER: I think we might have misled Dr. Bartlett a little bit in the slide which showed a 58 per cent mortality in umbilical hernia. That percentage was not an operative mortality but was the average mortality among all patients who entered the hospital with a diagnosis of strangulated umbilical hernia. It was included purely to show the lethal effect of umbilical hernia. I do not know offhand how many were moribund on admission. Some hernias were treated conservatively, including one or two umbilical hernias. There were a few cases in which strangulated femoral hernia had been actually missed.

As to Dr. Orr's question about those patients who were not operated on—there is a chance that we are likely to have made errors, but I will say that I went over

personally (along with the residents) the histories of more than 2,000 cases in which the diagnosis was intestinal obstruction. We eliminated those patients who we thought had ileus or peritonitis or adynamic ileus and accepted those who we felt had definite simple obstructions. Not all patients who get well from simple obstruction have just ileus, because we also happen to know that some of these patients were treated five or six times with suction and on the sixth time they had a strangulating lesion. So they did not have adynamic ileus the first time, but they had a simple obstruction then and later on a strangulating lesion.

You cannot make the flat statement that everybody who gets well without surgical treatment had an adynamic ileus and not a simple obstruction. Of course, we may have been in error in some. There is no way of telling, and likely some of those whom we accepted had not simple obstructions. But after reviewing each history and all the findings that went along with it, we accepted them. We discarded almost 1,000 cases diagnosed as examples of simple obstruction because we didn't think the diagnosis was correct.

Dr. McGraw asked about the type of anesthesia. Although our studies to date are not complete, it is my impression that spinal anesthesia was used in at least 90 per cent of the cases.

PLEUROPULMONARY MANIFESTATIONS OF AMEBIASIS

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AND
ROBERT T. FOX, M.D.
CHICAGO

DURING the past year, we have seen on the thoracic surgery service at Hines 10 cases of amebiasis. These came to our service only because their principal complaints or findings were referable to the chest. It is the purpose of this paper to call attention to the considerable amount of amebiasis now being seen and to point out that this amebiasis may appear in bizarre forms simulating common lesions of the chest. A survey of the literature of recent years has disclosed only a few scattered articles by authors in such endemic areas as India, Africa, Australia, and Brazil reporting single cases of pleuropulmonary amebiasis. In 1938 Keeton and Hood [1] at the University of Illinois reported 5 cases collected by them over a three year period. In 1936 Ochsner and DeBakey [2] reported a series of cases in New Orleans.

Of the 10 patients seen by us, 4 were admitted directly to our service, 2 were transferred from the medical service, and 4 were seen in consultation on the medical service. The preliminary or admitting diagnoses based on a brief history and examination were as follows: in 4 cases, pneumonia; in 2, empyema, and in 1 each, pulmonary abscess, appendicitis, peptic ulcer and cholecystitis. Six representative cases will be briefly described at this time with reproductions of their roentgenograms before us.

From the Thoracic Surgery Service, Veterans' Administration Hospital, Hines, Ill., and the Department of Surgery, Northwestern University School of Medicine.

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This article is published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans' Administration, who assumes no responsibility for the opinions expressed and the conclusions drawn by the authors.

1. Keeton, R. W., and Hood, M.: Symposium on Pneumonia: Pulmonary Disease Secondary to Amebiasis, M. Clin. North America **22**:27-43 (Jan.) 1938.

2. Ochsner, A., and DeBakey, M.: Pleuropulmonary Complications of Amebiasis: Analysis of One Hundred and Fifty-Three Collected and Fifteen Personal Cases, J. Thoracic Surg. **5**:225-258 (Feb.) 1936.

REPORT OF CASES

CASE 1.—This patient was admitted seriously ill with fever, cough, dyspnea, pain in the right side of the chest of six days' duration and diarrhea of three days' duration. He was slightly jaundiced and showed physical signs of effusion at the base of the right lung. His liver was palpable 4 cm. below the right costal margin but was not tender. A bedside roentgenogram of the chest showed elevation of the right side of the diaphragm and evidence of pleuritis at the base of the right lung. A history of service in the South Pacific with recurrent, mild attacks of diarrhea, combined with his present symptoms, suggested amebiasis with ruptured hepatic abscess. Specific therapy was temporarily withheld while attempts were made to isolate amebas in the stools. However, the patient's condition rapidly deteriorated, and although administration of emetine hydrochloride was started on the fifth day,

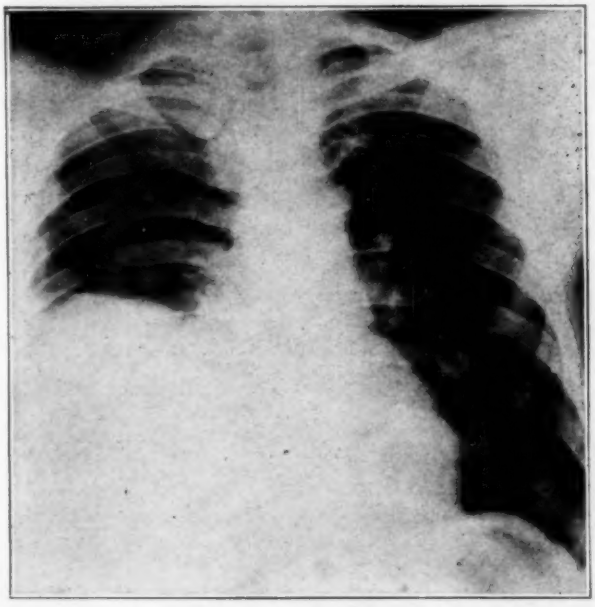

Fig. 1 (case 2).—Marked elevation of right side of diaphragm with relatively clear costophrenic angle.

he died on his seventh day in the hospital. Autopsy showed extensive amebic ulceration of the colon and ruptured hepatic abscess with subphrenic abscess.

CASE 2.—The patient had had chills, fever, cough and pain in the right side of the chest of increasing severity for three weeks prior to admission and his disease was diagnosed as pneumonia. He showed no improvement on penicillin therapy and in a few days began to expectorate large quantities of "catsup-like sputum." Ruptured subphrenic abscess with bronchial fistula was recognized, and he was transferred to our service, where immediate open drainage of the right anterior subphrenic space was instituted. He showed rapid improvement following drainage, and the cough and expectoration soon disappeared. The sputum showed an organism suggestive of ameba, and a course of emetine hydrochloride was given.

Amebas were also found after many examinations of the pus from the subphrenic space. After emetine therapy, drainage almost stopped but later increased in amount; it was finally completely checked by administration of a second course of emetine hydrochloride followed by chiniofon.

CASE 3.—This man was transferred to us from another veterans' hospital with the diagnosis of probable pulmonary abscess. His symptoms dated back approximately seven months. On arrival here, he was emaciated and seriously ill, and expectorated about a quart (0.94 liter) of "catsup-like sputum" daily. Regular roentgenograms of the chest showed no obvious source of this sputum, nor was a bronchogram helpful in demonstrating any pathologic condition. A diagnostic pneumoperitoneum was performed, demonstrating obliteration of the subphrenic space anteromedially. Although no amebas could be found in the sputum, a course

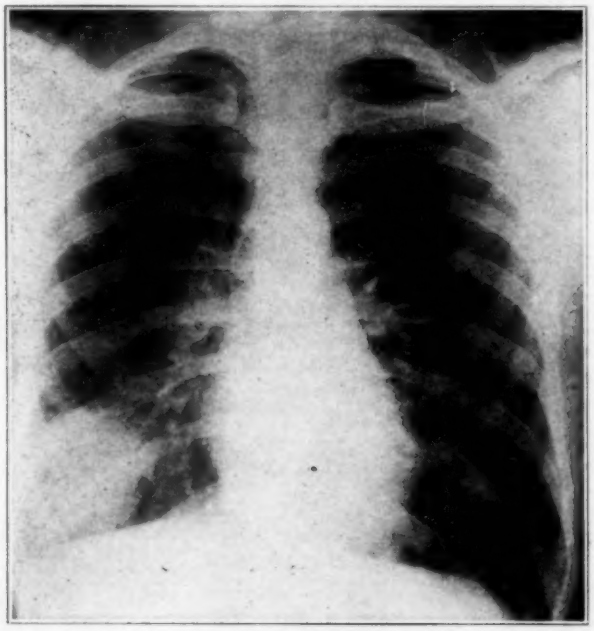

Fig. 2 (case 4).—A large round mass is seen in the lower pulmonary field on the right, and on lateral view is found to be posterior and separated from the diaphragm by a thin layer of aerated lung.

of emetine hydrochloride was given, followed by rapid improvement of symptoms and cessation of expectoration. The patient was soon discharged well.

CASE 4.—This patient, also a South Pacific veteran, had an attack of cough, expectoration, night sweats, hemoptysis and loss of weight early in 1946, and his disease was diagnosed by his private physician as virus pneumonia. He improved and returned to work, but in September the same symptoms returned and he was admitted to the Veterans' Administration Hospital at Hines. A roentgenogram taken in January 1946 showed only a moderate elevation of the right side of the diaphragm. Roentgenograms taken on his admission in September showed a round mass in the right lower posterior pulmonary field which could be interpreted as

abscess, tumor or possibly tuberculoma. Bronchograms showed only a space-occupying lesion in this area. On suspicion, emetine hydrochloride was given, and in a period of less than six weeks the lesion completely disappeared. A pneumoperitoneum showed a clear right subphrenic space. Sputum and stools were all negative for amebas. The patient was discharged well.

CASE 5.—This patient had the typical, acute pneumonia picture of chills, fever, cough and vomiting. Sulfadiazine and penicillin had little effect on his symptoms, and after two weeks he began to expectorate copious amounts of "anchovy-sauce" sputum. Amebiasis was then suspected, and a course of emetine hydrochloride was administered, followed by prompt relief of symptoms and the disappearance

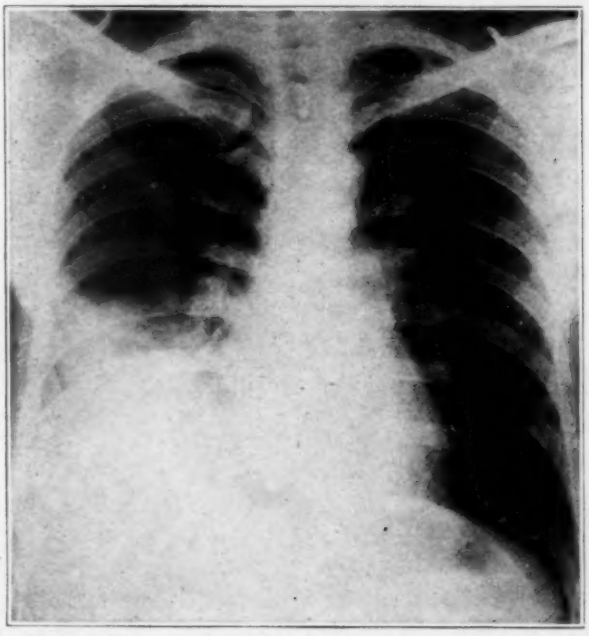

Fig. 3 (case 5).—There is partial obliteration of lower third of right pulmonary field. The diaphragm was not definitely visualized, but was thought to be fixed on fluoroscopic examination.

of the cough and expectoration. No amebas were found in the sputum, but a specimen of stool contained amebas.

CASE 6.—This young South Pacific veteran had an attack of pain in the right shoulder, followed in a few days by anorexia, pain in the lower part of the chest and the upper part of the abdomen on the right side and general malaise. He gradually became short of breath and showed increasing fever. His physician diagnosed empyema, aspirated about 1,000 cc. of bloody fluid from the right side of his chest and then advised hospitalization. A roentgenogram on admission, one month after onset of symptoms, showed the diaphragm high on the right side and a clear pulmonary field above, indicating that the aspirated fluid had come from the subphrenic space rather than the pleural cavity. Aspiration was performed here

on several occasions with air replacement, thus demonstrating a huge subphrenic space and apparently marked hepatic destruction. Roentgenograms showed two large subphrenic cavities with fluid levels, and a roentgenogram taken in the left decubitus position helped further to outline the extent of these cavities. Amebas could not be found in the aspirated fluid, but a course of emetine hydrochloride was given; this was followed by immediate relief of symptoms and return of temperature to normal. The subphrenic cavities were gradually becoming obliterated, but before final results could be evaluated, the patient, feeling well, left the hospital and failed to return for check-up.

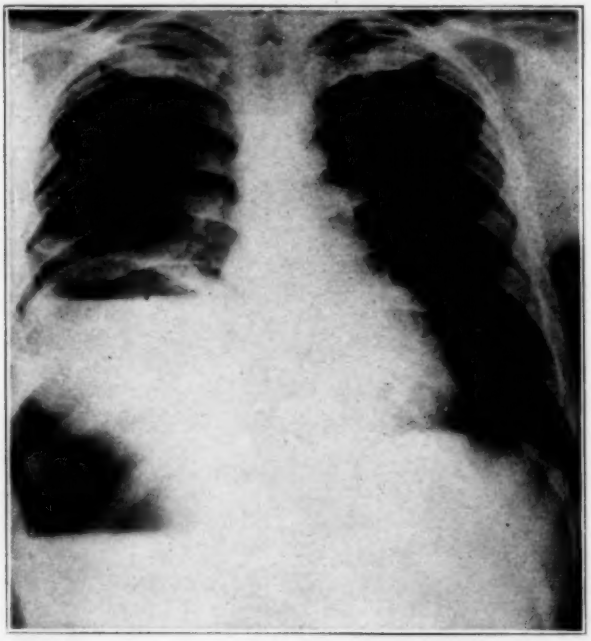

Fig. 4 (case 6).—The right side of the diaphragm is very high. Bloody fluid (1,500 cc.) has been aspirated from the subphrenic space and partially replaced by air. Note two separate fluid levels.

COMMENT

It is obvious from review of these cases that no typical picture or syndrome can be described. About the only common finding in all cases is roentgen evidence of elevation of the right side of the diaphragm. History of previous significant dysentery was unusual, but a period of service in North Africa or the South Pacific was in the record of all but 2. Demonstration of amebas in the sputum, stool or aspirated fluid was made in less than half of the patients. These cases have clearly shown that an amebic abscess can rupture into the subphrenic space, perforate the muscular barrier of the diaphragm and even rupture into a bronchus without causing either general peritonitis or empyema.

SUMMARY

The following points may be stressed: Amebiasis is being seen fairly frequently, especially in veterans of the North African or South Pacific theaters. Some of these cases of amebiasis may present findings typical of common diseases of the chest. After a reasonable effort is made to rule out the common lesions of the chest in such cases, one should suspect amebiasis and start specific treatment without further delay. Demonstration of the amebas is frequently impossible, and diagnosis must be based on favorable response to emetine hydrochloride therapy. The treatment of choice is a course of emetine hydrochloride, repeated if necessary, and supplemented by an orally administered amebicide and by aspiration if indicated to relieve symptoms of pressure. Early surgical drainage is not indicated and, in fact, may serve to delay recovery.

SOME PHYSIOLOGIC AND BIOCHEMICAL ALTERATIONS INCIDENT TO SURGICAL INTERVENTION

Report of a Case

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THE SURGEON is often presented with a deranged metabolism in patients who have undergone surgical treatment. The derangement may be due to the damaging effects of the operation itself or to a combination of the basic disease process, the operation and other complicating factors such as starvation or salt imbalance. Although knowledge of the metabolic disturbances which take place after operative procedures is admittedly highly important, the literature on this subject is fragmentary and incomplete. As a rule, only a few aspects of the physiologic process in the patient have been studied, such as organic function or tissue electrolytes, and then only in complicated cases. Accordingly, it was felt desirable to make as thorough a study as possible of the physiologic and biochemical changes which take place during and after operation.

The selection of the patient for a composite study of this type was an important consideration. Such a patient should be essentially normal with respect to metabolism and bodily function and should have undergone an operation in which transfusions are usually not absolutely required and yet one in which loss of blood and surgical trauma were substantial. It is important that accurate measurements of loss of blood be made operatively and postoperatively. A consideration of all these factors led us to select a patient subjected to radical mastectomy as the one for study.

The next question to be dealt with was the one of what should be studied. There are limitations in the number of blood specimens which can be removed from a patient without a subsequent transfusion being required. Also, the number of foreign substances used in clinical tests which can be administered simultaneously should be reduced to the minimum because of ignorance of their combined effects in the human

From the Departments of Surgery and Biochemistry, University of Chicago. Aided by a grant from the Otho S. A. Sprague Memorial Institute.

being. However, the selection of analyses was influenced mostly by the evidence in the literature and by the clinical experiences of surgeons therein. It was felt that a study should be made of the hematologic alterations, changes in body fluid, acid-base metabolism and nitrogen metabolism. The study was organized to provide some information on each of these aspects.

PLAN OF STUDY

All noncoagulated blood was collected in bottles containing dried heparin. All serum specimens were collected under oil. Urine was collected with toluene as the preservative. Blood volume was determined according to the method of Gregerson.[1] All specimens of blood were collected without stasis, and for the hematocrit readings the specimens were centrifuged for at least thirty minutes at 3,000 revolutions per minute.

Preoperatively, determinations were carried out for chlorides,[2] p_H [3] carbon dioxide content,[3] total base,[4] nonprotein nitrogen,[3] blood urea nitrogen,[3] total protein [3] and albumin and globulin.[5] Hematologic studies included red blood cell counts, hematocrit readings and determinations of the hemoglobin content.[6] The blood volume [1] and the extracellular fluid volume [7] were likewise determined. Many of these determinations were repeated two, five and ten hours after the operation and on the first, second and third days postoperatively. Records were kept of the fluid balance, intake of food and loss of blood.

The red blood cell counts were done in triplicate and all chemical analyses done in duplicate.

REPORT OF A CASE

A 56 year old housewife had noticed a lump in her right breast for the past year. One month prior to her admission to the hospital this lump began to enlarge slightly. At the same time her entire breast began to enlarge and appeared inflamed and slightly tender. The patient had otherwise been in good health, and the rest of the history was noncontributory.

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1. Gregerson, M. I.: Practical Method for Determination of Blood Volume with Dye T-1824: Survey of Present Basis of Dye-Method and Its Clinical Applications, J. Lab. & Clin. Med. **29**:1266-1286 (Dec.) 1944.

2. Wilson, D. W., and Ball, E. G.: A Study of the Estimation of Chloride in Blood and Serum, J. Biol. Chem. **79**:221-227 (Sept.) 1928.

3. Peter, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2.

4. Gamble, J. L.: Chemical Anatomy, Physiology and Pathology of Extracellular Fluid: A Lecture Syllabus, Boston, Spaulding-Moss, 1941.

5. Campbell, W. R., and Hanna, M. I.: The Albumins, Globulins and Fibrinogens of Serum and Plasma, J. Biol. Chem. **119**:15-33 (June) 1937.

6. Evelyn, K. A.: Stabilized Photoelectric Colorimeter with Light Filters, J. Biol. Chem. **115**:63-75 (Aug.) 1936.

7. Crandall, L. A., Jr., and Anderson, M. X.: Estimation of the State of Hydration of the Body by the Amount of Water Available for the Solution of Sodium Thiocyanate, Am. J. Digest. Dis. & Nutrition **1**:126-131 (April) 1934.

Physical examination revealed a well nourished and well developed white middle-aged woman, weighing 60 Kg., who did not appear ill. The lungs and heart were apparently normal. Her blood pressure was 180 systolic and 70 diastolic. Her right breast in the upper outer quadrant contained a 7 cm. rounded hard mass, with its periphery meeting that of the areolar border. The nipple was slightly retracted. The right breast was larger than the left. Several small axillary lymph nodes were palpable.

The results of laboratory examinations, which are in the main discussed elsewhere, were essentially normal. Roentgenograms of the chest and long bones were normal.

A radical mastectomy was performed, without any untoward incident. Her blood pressure at the beginning and conclusion of the operation was 100 systolic and 60 diastolic. Her pulse rate was 100 immediately prior to operation and 80 at the finish of operation. Her respiratory rate remained in the region of 34. An infusion of 1,500 cc. of isotonic solution of sodium chloride was given during the surgical procedure. The operative loss of blood was 550 cc.

Except for a pallid appearance, the patient made an uneventful recovery. The wound healed normally. On the first four postoperative days the patient had some nausea and occasionally vomited. The nausea was coincident with the intravenous injection of thiocyanate.

Pathologic examination of the breast and axillary tissue disclosed widely infiltrating scirrhous carcinoma. A total of thirty diffusely infiltrated lymph nodes were dissected out from the axillary fat.

RESULTS AND COMMENT

The data have been grouped for convenience of discussion into sections on the hemodynamic process, acid-base metabolism, changes in body water and nitrogen metabolism.

The alterations in the hemodynamic process have been illustrated in figure 1. Although there is a considerable reduction in the red cells, hematocrit reading and hemoglobin content from preoperative levels, these values alone do not indicate the full extent of the changes in the composition of the blood. Thus, in spite of a 1,200 cc. loss of blood from the operation and the withdrawal of samples over a three day period, the volume is maintained at approximately preoperative levels by a compensating increase in plasma volume. If the blood volume had not been replaced by the increase in plasma volume, the blood count would obviously remain unchanged. Therefore, the reason for the drop in the red blood cell count is hemodilution of the residual blood.

The body can deliver rapidly large amounts of plasma protein to the blood stream after acute hemorrhage,[8] which accounts for the increase in plasma volume. Even though the plasma protein concentration was observed to fall (see table), total circulating protein remained constant. Since blood hemoglobin cannot be replenished as rapidly as plasma protein, one can understand the precipitous fall in total circulating hemo-

8. Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source, Production and Utilization, Physiol. Rev. **20**:194-217 (April) 1940.

globin and in red cell mass. In any consideration of postoperative anemia it is important, therefore, to follow the changes in the red cell mass and in total circulating hemoglobin, as the red blood cell count alone may be misleading. A low count might therefore signify either an actual lack of the formed elements or an increase in the plasma volume.

Rapid changes in acid-base metabolism were observed as shown in figure 2. The precipitous fall in total carbon dioxide content and the

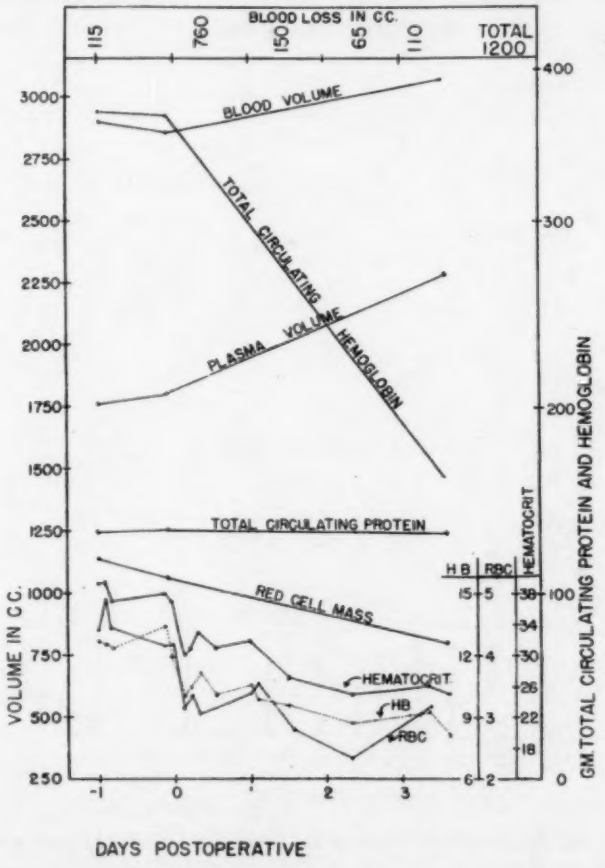

Fig. 1.—Illustration of hemodynamic changes incident to surgical intervention.

shift toward acidity as shown by lower p_H values occur without accompanying pronounced changes in total base. These observations are interpreted as the result of an excess of acid, which is probably due to lactic acid which accumulates in hemorrhagic shock.[9] The alterations in chloride content are regarded as compensating for the increase in acid

9. Nash, J.: Surgical Physiology, Springfield, Ill., Charles C Thomas, Publisher, 1946.

radicals, according to Gamble.[4] The change in carbon dioxide content may possibly be regarded as an early sign of impending hemorrhagic shock.

Total body water has been determined with the use of sulfanilamide, but in view of its plasma-binding properties [10] and of the irregular results obtained, this variable has not been included in our consideration of changes in body water. More reliance can be placed on the measurement of extracellular fluid with thiocyanate. Results obtained with this method have been represented in figure 3. The interstitial fluid is

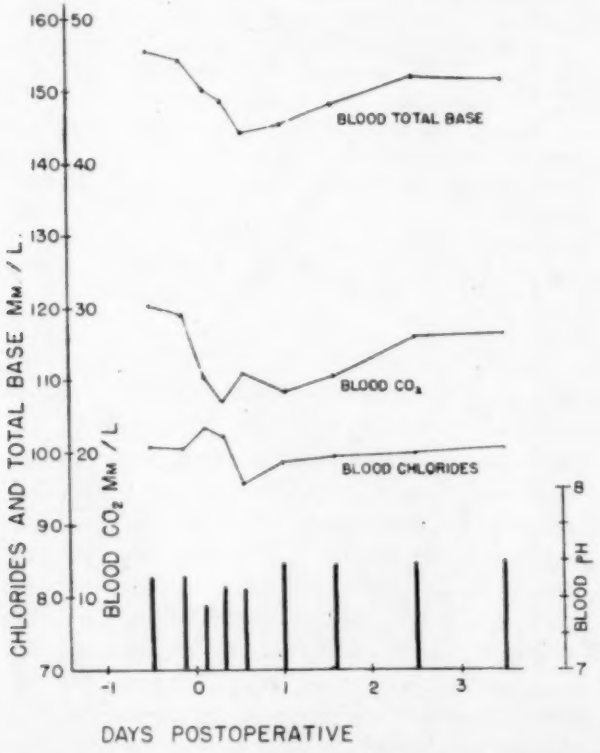

Fig. 2.—Some alterations occurring in acid-base metabolism are shown.

calculated by subtracting plasma volume from extracellular fluid volume. For purposes of comparison, the variations in the chloride content of body fluid have been included. The extracellular and interstitial fluid markedly increased postoperatively without concomitant changes in the chloride content. This observation, as well as those of others,[11] shows the fallacy in attempting to assess the state of body fluid from

10. Peters, J. P.: Water Exchange, Physiol. Rev. **24**:491-531 (Oct.) 1944.

11. Abbott, W. E.: Surgery: A Review of the Present Concepts on Fluid Balance, Am. J. M. Sc. **211**:232-239 (Feb.) 1946.

determinations of serum chloride. From a knowledge of the approximate intake of salt and of the actual amount of chloride excreted in the urine or lost from venipuncture, we have found postoperative retention of sodium chloride. This would explain the augmentation of extracellular fluid postoperatively.

Sodium chloride intolerance has been observed in surgical patients by Coller.[12] Ariel and others [13] have likewise observed chloride retention in hypoproteinemic patients with cancer undergoing surgical treatment.

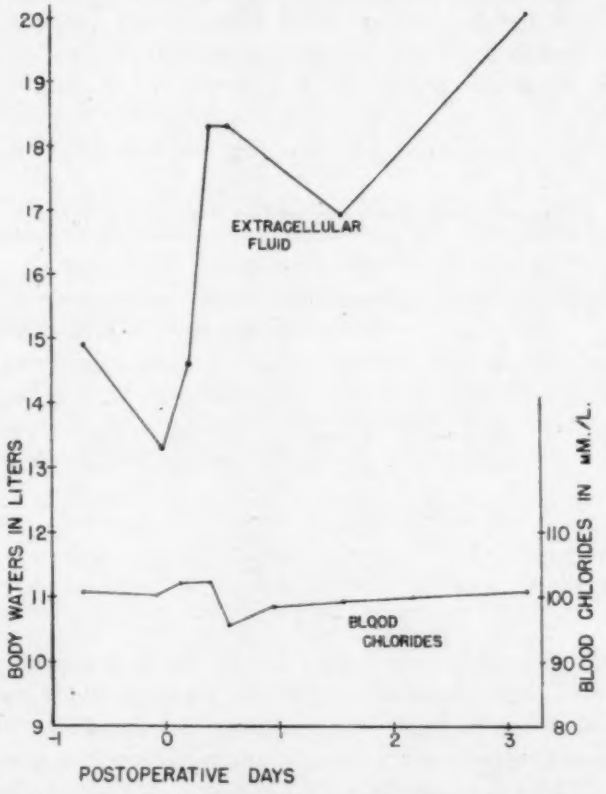

Fig. 3.—A comparison of changes in serum chloride and extracellular fluid.

The studies were performed on patients whose metabolism was certainly abnormal preoperatively. It is possible that in a patient such as ours, whose general condition was relatively normal, chloride retention may

12. Coller, F. A.: Post-Operative Salt Intolerance, Ann. Surg. **119**:533-542 (April) 1944.

13. Ariel, I.; Abels, J. C.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies of Patients with Cancer of Gastrointestinal Tract: Treatment of Hypochloremia Refractory to Administration of Sodium Chloride, Especially in Patients with Gastrointestinal Cancer, J. A. M. A. **123**:28-30 (Sept. 4) 1943.

develop postoperatively, a fact which has not received adequate attention in the literature to date. Administration of isotonic solution of sodium chloride should be undertaken with caution to avoid overdosage postoperatively.

From the accompanying table it is evident that immediately after the operation the plasma protein concentration dropped about 2 Gm. per hundred cubic centimeters from good preoperative levels. Some return toward normal values occurred, but the patient by the third postoperative day had lower protein levels than before operation.

In view of the deficiencies of the conventional methods for determining albumin and globulin, pointed out elsewhere,[14] no significance is attached to the small changes in the albumin and globulin fractions.

Although the nonprotein nitrogen content of the blood shows little change, the urea nitrogen is definitely increased over preoperative levels.

Nitrogen Metabolism as Related to Surgical Intervention

Time		Non-protein Nitrogen, Mg./ 100 Cc.	Blood Urea Nitrogen, Mg./ 100 Cc.	Total Protein, Gm./ 100 Cc.	Albumin, Gm./ 100 Cc.	Globulin, Gm./ 100 Cc.	Albumin-Globulin Ratios
Day	Hour						
1 day preoperatively	9 a.m.	41.8	8.8	7.6	4.7	2.9	1.6
Day of operation	7 a.m.	27.2	8.0	7.7	3.9	3.8	1.0
	9:30 to 12:30	operation					
	12:30 p.m.	27.5	8.6	5.8	3.6	2.2	1.6
	5:30 p.m.	28.0	15.4	6.5	3.9	2.6	1.5
	10:45 p.m.	26.4	....	6.3	4.0	2.3	1.7
1 day postoperatively	9:30 a.m.	33.5	11.2	6.3	3.8	2.5	1.5
	11:40 p.m.	31.4	17.6	6.7	4.2	2.5	1.7
2 days postoperatively	9 a.m.	30.0	14.0	6.7	4.5	2.2	2.0
3 days postoperatively	9 a.m.	29.1	16.9	6.0	4.1	1.9	2.1

It is difficult to explain this finding on the basis of any single factor, although increased catabolism of protein seems a likely explanation. On the basis of the hippuric acid and urea clearance tests which were done, no marked impairment of hepatic and renal function was observed.

From a consideration of the hemodynamic changes and the plasma protein levels, it is clear that the maintenance of the blood volume is an important mechanism in resisting operative trauma and shock. Since the plasma volume is determined in large part by its protein content, which is affected by preoperative protein reserves and postoperative toxic loss, the maintenance of blood volume and especially the replacement of lost cell volume by plasma may be considered in part a physiologic function of protein metabolism.

14. Fishman, W. H., and LeVeen, H. H.: A Method of Partitioning Liver Proteins and Its Application to the Study of the Effects of Acute Hemorrhage in the Dog, to be published.

The chief value of the present study is that it presents a composite picture of many of the physiologic changes which take place after surgical treatment. From the case presented it is possible to see more clearly some of the important problems for further investigation. These are (1) the explanation of the pronounced diminution in the number of formed elements in the blood, (2) an understanding of the shifts in electrolytes and water in tissues and (3) a knowledge of the factors which maintain the level of blood proteins. Confirmatory studies designed to investigate certain of these problems in more detail are now in progress.

SUMMARY

A composite chemical and physiologic study is reported on a patient undergoing radical mastectomy. Among the more striking effects which were apparent were hemodynamic changes and alterations in the fluid balance, acid-base metabolism and nitrogen metabolism. There was a considerable reduction in the red blood cell count, hematocrit reading and hemoglobin content from preoperative levels, with the blood volume having been maintained. The extracellular and interstitial fluid showed distinct increases without concomitant changes in serum chloride. There was an appreciable shift toward acidosis immediately after the operation. The blood protein content dropped and was still below preoperative levels three days after the operation. The implications have been pointed out and discussed.

GIANT SARCOMA OF THE PLEURA

Report of a Case

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AND

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HINES, ILL.

THE EXPLORATORY thoracotomy is being employed with increasing frequency in cases of disease of the chest in which the usual routine examinations fail to establish a diagnosis. This serves to stimulate interest in thoracic tumors, practicularly those tumors which if recognized early can be subjected to surgical extirpation with excellent chances for a cure. Prominent in such a group are the localized fibroblastic tumors of the pleura of which the following case is illustrative.

REPORT OF A CASE

J. P., a 55 year old Negro man, entered the hospital Aug. 8, 1946, complaining of edema of the ankles for the previous four years and dyspnea and palpitation on exertion for the previous six months. He also had abdominal discomfort and flatulence. He had been taking digitalis under direction of a private physician. He had a cough, productive of frothy sputum, usually worse at night. There was no history of pain in the chest. His past history was essentially negative.

Physical Examination.—Physical examination disclosed an obese Negro man in no distress. The eyes, ears, nose and throat were normal on physical examination. The blood pressure was 120 systolic and 80 diastolic, the pulse rate 92, the rhythm regular, the apex beat in the fifth interspace, 1 cm. outside the nipple line and the right border 3 cm. to the right of the right sternal border. There was a visible lag of the left side of the chest with decreased fremitus and absent breath sounds over the lower half of the left side of the chest. The area was dull to percussion. The liver was palpable 3 fingerbreadths below the costal margin. The spleen was not palpable. There was no tenderness or rigidity. The reflexes were normal.

Laboratory Data.—The red blood cell count was 4,000,000, the hemoglobin reading 80, the white blood cell count and the differential count normal. The urine was

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From the Department of Pathology, Veterans' Administration Hospital, Hines, Ill.

Read at the fourth annual meeting of the Central Surgical Association, Chicago, Feb. 20, 1947.

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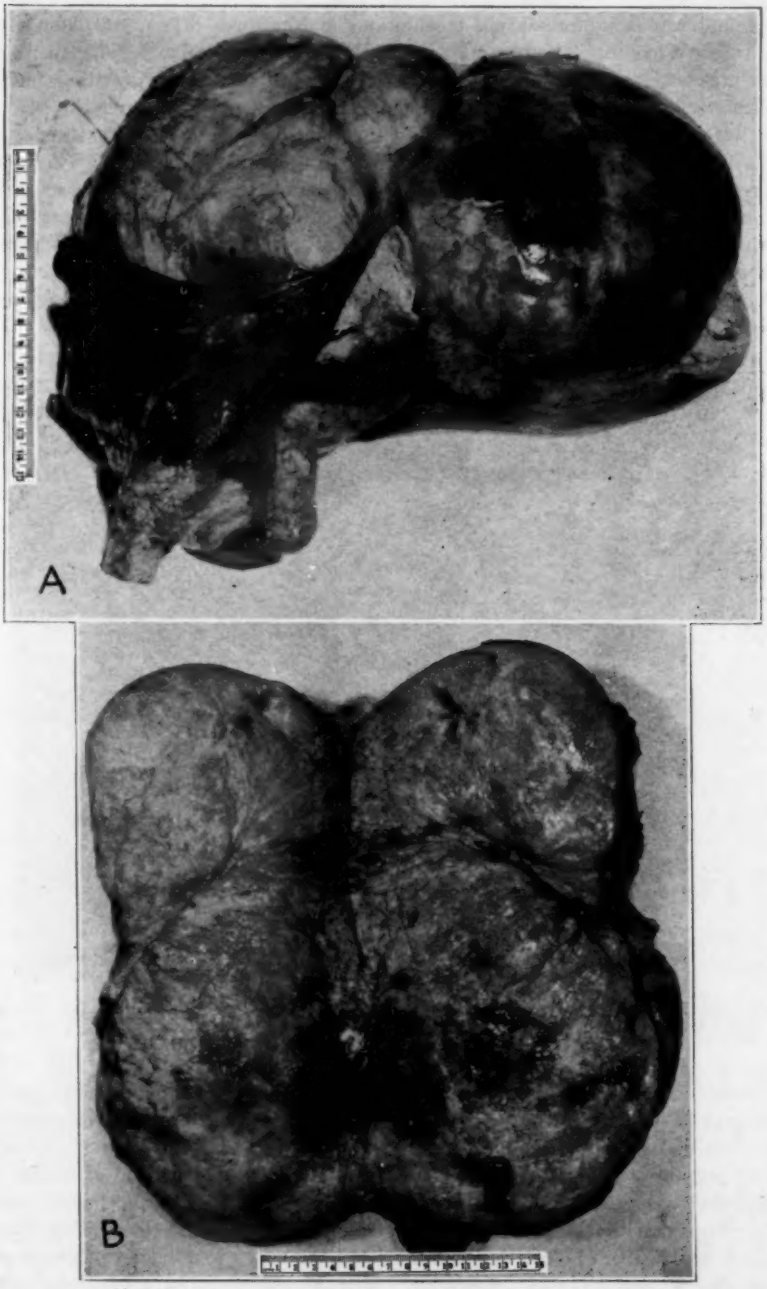

Fig. 1.—*A*, pleural tumor compressing lung medially. Note smooth lobulated appearance. *B*, cut section of tumor showing lobulation, encapsulation and areas of softening with hemorrhage.

essentially normal. The sedimentation rate was 28 mm. per hour. Repeated twenty-four hour specimens, guinea pig inoculations and cultures of sputum did not produce tubercle bacilli. The pleural fluid was repeatedly negative for organisms and tumor cells. The prothrombin time was normal. The electrocardiogram was abnormal, the tracing nonspecific. The roentgen report of September 14 was: "The left side of the chest was completely opaque. The mediastinal structures were displaced to the right. The left side of the diaphragm appeared normal. There were no areas of pneumothorax." A bronchogram on October 21 showed trachea and left main bronchus to be displaced to the left and a dense opacity occupying all the left side of the chest. The heart was displaced to the right. Differentiation between mass and fluid could not be made. On December 21, "a soft oval density at the level of the right first anterior interspace suggestive of a metastatic lesion was seen within the over-all homogenous opacity of the left side of the chest."

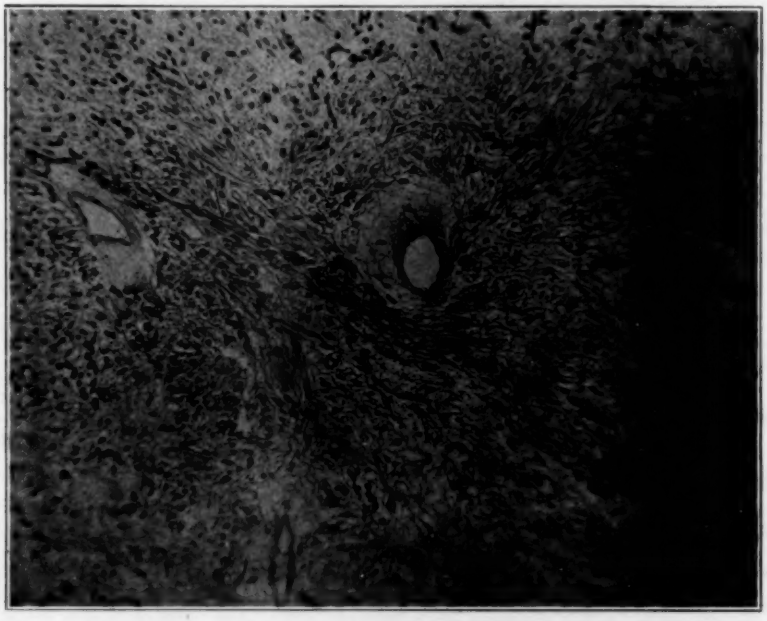

Fig. 2.—Section of tumor, showing loosely disposed spindle cells with a heavy intercellular collagen matrix (× 100).

Course.—The patient became comfortable on cardiac management, and the edema of the ankles promptly disappeared. Several thoracenteses were performed; not more than 400 cc. of clear fluid was recovered. Auricular fibrillation was occasionally present for short periods. The Tumor Board on October 23 expressed the opinion that the patient had a bronchogenic tumor, probably of the upper lobe of the left lung and the left main bronchus, and roentgen therapy to the left side of the chest was instituted. Administration of codeine every four hours was necessary for cough and embarrassed respiration. The patient suffered a "fainting spell" on December 27 and died rather suddenly a few hours later. Postmortem examination disclosed an obese Negro man weighing 300 pounds (136.1 Kg.); his age was 55 years. There was no palpable lymphadenopathy. Pigment changes and loss of hair due to irradiation were noted in the skin over the sternal area.

Examination of the chest showed an enormous tumor mass almost filling the left pleural cavity. There was 800 cc. of clear straw-colored fluid. The tumor weighed 4,600 Gm. and measured 28 by 16 by 14 cm. It was covered with a shiny gray translucent capsule which was continuous with the parietal pleura at the point of attachment to the posterior wall. The point of attachment measured 5.5 cm. across. There was also a small point of attachment to the diaphragm which was easily separated, leaving the diaphragmatic pleura intact. The left lung was completely collapsed medially, displacing the pericardial sac to the midline. The lung was airless. Cut section of the tumor disclosed a lobulated solid gray homogenous mass which cut with resistance. The cut surface was glistening grayish white with an occasional small hemorrhagic area. The lymph nodes of the mediastinum were not involved, and no evidence of metastasis was noted.

The heart weighed 480 Gm. The muscle was friable and of poor consistency. There was some dilatation of the right side. No valvular lesion was noted. There was minimal arteriosclerosis. The right lung was normal. The abdominal organs, including the gastrointestinal and genitourinary tracts, showed no gross pathologic lesion.

Microscopic examination of the tumor disclosed a spindle cell growth. The cells resembled the fibroblast. The nuclei were elongate with a fine chromatin network and minute nucleoli. By the use of phosphotungstic acid and hematoxylin stain fibroglia fibrils were seen attached to the ends of the spindle cells. The cells were separated by collagen fibrils forming a matrix and in some areas tended to grow in bands or bundles. Smooth muscle cells were not identified.

COMMENT

Lichtenstein [1] (1931) furnished a detailed study of the literature dealing with primary tumors of the pleura. He found 31 cases of malignant tumors arising from the subpleural connective tissue of the pleura. He found that according to their clinical course they fall into three groups. The first two groups are frankly malignant in both their histologic appearance and their behavior. The tumors of the third group show a histologic structure which would classify them as malignant, but are benign in their clinical course. They show no tendency to metastasize or recur, and they do not show the toxicity of truly malignant tumors. They do not cause the typical cachexia and anemia. Lichtenstein found 8 such cases in the German literature. It is in this third group of Lichtenstein's classification that the case described in this paper would be placed.

MacMahon and Mallory [2] (1928) reported slowly growing primary fibrosarcoma of the pleura.

Klemperer and Raben [3] (1931) reported three giant fibrosarcomas of the pleura, and one lipoma. They noted that although these tumors

1. Lichtenstein, H.: Die Klinik und Pathologie der primären Pleuratumoren, Deutsche Ztschr. f. Chir. **233**:29-46, 1931.

2. MacMahon, H. E., and Mallory, G. K.: Fibrosarcoma of the Pleura: Report of a Case, Am. J. Path. **4**:387-394, 1928.

3. Klemperer, P., and Rabin, C. B.: Primary Neoplasms of the Pleura: A Report of Five Cases, Arch. Path. **11**:385-412 (March) 1931.

present histologic evidence of low grade malignancy they usually progress slowly and usually cause death by interference with pulmonary circulation. Furthermore, they offer an opportunity for surgical removal.

In 2 of the 3 cases of giant primary fibrosarcoma of the pleura described by these authors aspiration was done. One case was discovered incidentally during a routine examination of the chest of a woman being prepared for a gynecologic operation. The large tumor was removed with good recovery. In the second case the tumor was only partially removed because of its size and extensive adhesions. Four years later the patient's symptoms recurred, and the tumor was again partially resected. In the third case the giant tumor gave a clinical history of at least twenty years' duration. Over a period of ten years the patient had been in the hospital five times with a diagnosis of aortic aneurysm and bronchial asthma. Pulmonary edema developed on the fifth admission; the woman died, and the giant tumor was discovered at autopsy.

Cabot Case 18452 [4] (1932) was of a slow growing fibrosarcoma of the pleura. A clinical diagnosis of tumor of the left pleural cavity was established. A thoracotomy was done, but the condition proved inoperable. Death followed four days later, and at autopsy the tumor was estimated to weigh 20 pounds (9,072 Gm.). In this case the clinical history was of five months' duration.

Fawcett [5] (1945) reported a large fibroma arising from the pleura of the lower lobe of the right lung. A clinical diagnosis of tumor was reached by means of roentgen examination and the finding of numerous endothelial-like cells, many undergoing mitosis in aspirated fluid. At operation the tumor, 12 cm. in diameter, was easily shelled out, and the patient made a good recovery.

In the case of massive primary fibrosarcoma of the pleura recorded in this paper the clinical picture of pulmonary and cardiac embarrassment was caused by pressure of the tumor.

SUMMARY

A case of giant primary fibrosarcoma of the pleura, presenting a clinical picture of pulmonary and cardiac embarrassment, is described. The diagnosis was established at autopsy.

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4. Incapacitating Dyspnea in an Unusual Chest Case, Cabot Case 18452, New England J. Med. **207**:843-847, 1932.

5. Fawcett, A. W.: Large Fibroma Arising from Pulmonary Pleura of Right Lower Lobe, Brit. M. J. **2**:425, 1945.